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UNIVERSITY COLLEGE HOSPITAL
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(UNIVERSITY OF LONDON.)



RESEARCH DEPARTMENT.

Director : Dr. CHARLES BOLTON.

COLLECTED PAPERS.

VOL. II.

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1

THE MECHANICAL CONTROL OF PNEUMO-
THORAX DURING OPERATIONS ON
THE CHEST,
*WITH A DESCRIPTION OF A NEW APPARATUS.**

THE unexampled increase in the possibilities of surgical treatment which followed upon an understanding of the causes of wound infection has been of universal applicability to all regions of the body, with one notorious exception—the thorax. The surgery of the nervous system, the bones, the joints, has grown more and more elaborate and enterprising and been able to set before itself higher and higher standards of efficiency, while the surgery of the thorax has until quite recently remained almost as primitive and timid as it had been before Pasteur and Lister. The reason is obvious enough. The principles of asepsis gave to the abdominal surgeon freedom of access to the diseased parts and allowed him to elaborate his measures against the actual disease, secure in the knowledge that the primary intervention was in itself practically free from risk. The possibility of carrying out a safe exploratory laparotomy once established, the development of abdominal surgery was assured. To the surgeon of the thorax, however, no such freedom of access was given. The execution of a safe and thorough exploratory thoracotomy was barred by an unsolved physiological problem of quite another sort.

A free opening of the abdomen in itself produces no disturbance in the functioning of the contained organs, whereas a free opening of the chest under ordinary conditions produces, by causing a complete collapse of the lung, an immediate and dangerous interference with the vital mechanisms which depend directly upon the integrity of the pleural cavities. Until the disturbance consequent upon a pneumothorax could be prevented, it was impossible for the surgery of the thorax fully to share in the general progress of the art.

As a preliminary to the consideration of this problem, an understanding of the elementary facts of the mechanism of respiration is essential. The respiratory movements are not concerned merely with the single function of the

* From the Research Laboratories, University College Hospital Medical School.

eration of the lungs, but contribute a factor essential to the normal maintenance of the pulmonary circulation and of considerable importance to that of the systemic. There are certain pronounced differences in the mechanics of the pulmonary and systemic circulations. The latter consists essentially of a pump driving blood under high pressure into an elastic reservoir, the arteries; and the current of blood is mainly influenced by variations in the elasticity of the latter affected through the vasomotor apparatus. The pulmonary circulation, on the other hand, consists of a pump driving blood under comparatively low pressure into a reservoir, the lungs, which is constantly varying in size with respiratory movements. This variation, moreover, in its effects on the circulation is an active one, drawing blood into the lungs during inspiration and expelling it during expiration. Thus the pulmonary circulation may be regarded as made up of two parts, each of which is in active pulsation, the ventricle impelling the blood onward with the rapid pulsations of the cardiac rhythm, while the lungs contribute the slower but more voluminous impulses of the respiratory cycle. It should be clear from the foregoing that interference with the pulmonary circulation will be produced by collapse of one lung,* and that although this lung might have its aerating capacity restored by mechanical inflation, the embarrassment of the pulmonary circulation would still remain unless the normal respiratory movements of the lung were re-established.

In this connexion it is appropriate to refer to the most obvious of the expedients that have been devised to maintain the function of the lungs after the chest has been opened. As long ago as the middle of the sixteenth century Vesalius¹ recognized the possibility of aerating the blood after the chest had been opened, by passing a continuous current of air through the lungs, whilst in 1667 Hook read before the Royal Society a paper entitled, "An Account of an Experiment made by Mr. Hook of Preserving Animals Alive by Blowing through their Lungs with Bellows,"² of which the following is an abstract:

I did heretofore give this Illustrious Society an account of an Experiment I formerly tryed of keeping a Dog alive after his *Thorax* was all display'd by the cutting away of the *Ribs* & *Diaphragm*; & after the *Pericardium* of the Heart also was taken off. But divers persons seeming to doubt of the certainty of the Experiment by reason that some Tryals of this matter made in some other hands, failed of success; I caus'd at the last Meeting the same Experiment to be shewn in the presence of the *Nobly Company*, & that with the same success, as it had been made by me at first: the Dog being kept alive by the *Respiration* blowing up of his Lungs with *Bellows*, & they suffered to subsist, for the space of an hour or more, after his *Thorax* had been so display'd, & his *Aspera Arteria* cut off just below the *Larynx*, & bound in upon the nose of the *Bellows*.

* We are here considering collapse of the lungs as such without reference to other parts of the mediastinum or other possible factors. ¹ Translated in the *British Society*, October 24th, 1667. Published in the *Philosophical Transactions*, 1667, page 539.

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And because some Eminent Physicians had affirm'd, that the *Motion of the Lungs* was necessary to Life upon the account of promoting the Circulation of the Blood, & that it was conceiv'd, the Animal would immediately be suffocated as soon as the Lungs should cease to be moved, I did (the better to fortifie my own *Hypothesis* of this matter, & to be the better able to Judge of several others) make the following additional experiment; . . . [Hook fixed another bellows unto the first so as to be able to keep up a constant blast of air.] This being continued for a pretty while, the dog, as I expected, lay still, his eyes being all the time very quick, & his heart beating very regularly. But upon ceasing this blast, & suffering the Lungs to fall & lye still, the Dog would immediately fall into Dying convulsive fits; but he as soon reviv'd again by the renewing the fulness of his Lungs with the constant blast of fresh Air. . . . [At the end of the operation Hook cuts off a piece of the lung and finding that the blood is still circulating in it says:] Which seem to be Arguments, that as the *bare Motion* of the lungs *without fresh Air* contributes nothing to the life of the animal, he being found to survive as well when they were not mov'd, as when they were; so it was not the subsiding or movelesness of the Lungs that was the immediate cause of Death, or the stopping the circulation of the Blood through the Lungs, but the *want* of a sufficient *supply of fresh Air*.

I shall shortly furthur try, whether the suffering the Blood to circulate through a vessel, so as it may be openly exposed to the fresh Air, will not suffice for the Life of an Animal; & make some other Experiments, which, I hope, will thoroughly discover the *Genuine use of Respiration*; & afterwards consider of what benefit this may be to Mankind.

Mechanical respiration, as is of course well known, has been used for a long time, and extensively in experimenting on animals for the inflation of the lungs when it is required to open the chest. It has proved of great value by lowering the high mortality that must necessarily result if the operations are carried out with the lungs collapsed and an uncompensated pneumothorax present. That the method is in itself the cause of a small percentage of the deaths that result from the experiments, is not a sufficiently great objection to outweigh its advantages. But in human beings such a danger must necessarily be an absolute contraindication.*

By means of mechanical respiration the lungs are rhythmically inflated by a current of air blown into the trachea and respiratory undulations in the arterial pressure are still produced. But the effect of the inpumping of the air in mechanical respiration (the substitute for inspiration) is exactly the reverse of that of a normal inspiration. In the latter, after the initial fall of blood pressure, there is a steady rise during the rest of inspiration, and continued into the beginning of expiration, and this is succeeded by a fall which continues until the next inspiration has begun. When the lungs are inflated mechanically, the intrathoracic pressure is increased instead of decreased, and the arterial pressure, after the initial rise, falls. Thus mechanical respiration reverses the normal influence of the respiratory movements on the pulmonary circulation. Such a reversal of the normal process is at least un-

*Tissler and Hallion speaking, however, of mechanical respiration, say: "The success of this method on animals justifies its use in man."

desirable, seeing how delicate the respiratory mechanism is known to be in many during anaesthesia. Mechanical respiration produces a condition of apnoea, and it is conceivable that the additional effect of the toxic influence of chloroform might prevent the centres from resuming their normal activities.

Further, interstitial emphysema is a not infrequent sequela of mechanical respiration.

The grave symptoms which follow when a large opening is made in the chest wall are not, however, entirely

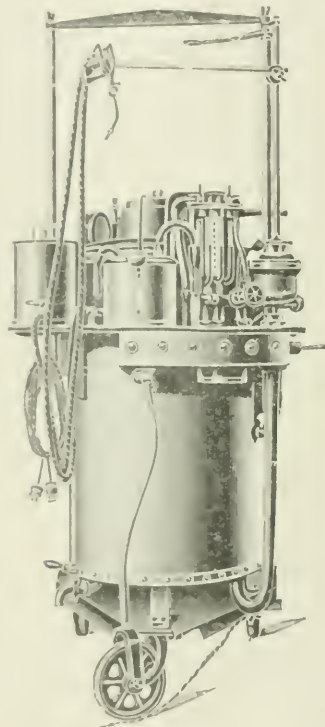


FIG. 1. Front view of author's hyperbaric chamber apparatus. Air chamber empty.

due to the loss of the physiological function of the lung: they are in part the result of the pathological complication of an open pneumothorax.

Garrod has shown that an opening in the chest wall produces no serious consequence in itself so long as the size of that opening is less than the size of the glottis. Air enters the pleural cavity with each inspiration and the lung collapses gradually, but this collapse is neither complete

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nor maintained. The lung by virtue of its elasticity is greatly reduced in size, yet with each inspiration and expiration there is some slight alteration in volume, and during forced expiratory efforts—for example, coughing—some of the air from the sound lung is forced over into and expands the collapsed lung. The amount of movement in the lung, though not great, assists in the maintenance of the pulmonary circulation and in the aëration of the blood passing through the collapsed lung, and further, the size of the thoracic opening is not sufficient to allow the

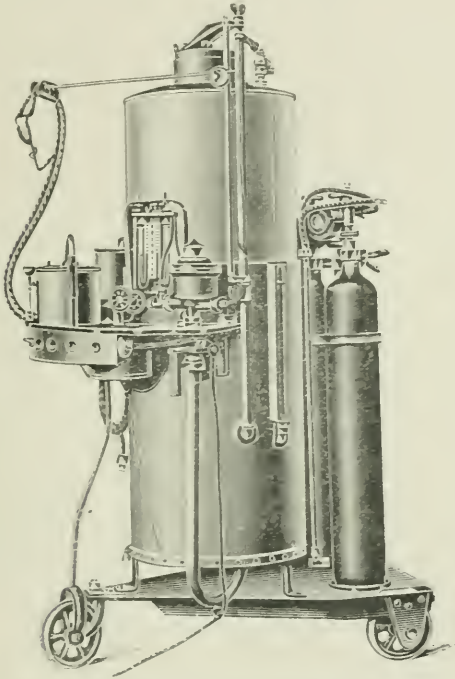


Fig. 2.—Side view of author's hyperatmospheric apparatus. Air chamber full.

mediastinum to flap to and fro. But when a large opening is made through the chest wall the lung at once collapses and the alarming symptoms of an uncompensated pneumothorax at once appear and progress to a fatal termination. Garré attributes the symptoms of an uncompensated pneumothorax—cyanosis, dyspnoea, and rapid irregular beating of the heart—to the flapping to and fro of the mediastinum and its contents, the heart, and large vessels, etc., with each inspiration and expiration. This to-and-fro flapping occurs as the result of the negative pressure between the pleural surfaces of the unaffected lung and

the atmospheric pressure on the mediastinum, which is not a rigid body. During inspiration, therefore, since the pressure in the sound lung is less than atmospheric, the mediastinum is pushed across to that side, but during expiration the intrapulmonary pressure is greater than atmospheric, and so the mediastinum is pushed back towards the affected side.

Sauerbruch,⁸ on the other hand, considers that this is not the most important cause of the cyanosis and dyspnoea of an uncompensated pneumothorax, and attributes these phenomena to the alterations in the pulmonary circulation produced by collapse and loss of movement of the lung.

The pulmonary circulation differs very considerably from the systemic, and is dependent on: (1) The force of the right heart. (2) The difference of the pressure in the pulmonary veins and arteries; this increases with the increase in negative pressure during inspiration and decreases during expiration. (3) The diameter of the vessels. (4) The pressure in the lung.

During expiration the difference in pressure between artery and vein is lessened, and associated with the increase of pressure in the lung the diameter of the vessels is diminished. But if the lung is collapsed as the result of an uncompensated pneumothorax there is loss of the most important influences controlling the pulmonary circulation on that side, and the forces which now act on the vessels are directly antagonistic to the proper aëration of the blood. Thus the absence of the intrathoracic variation of pressure on the affected side prevents the constant alteration in the difference in pressure in the pulmonary veins and arteries, and in the alveoli and alveolar vessels, while the alveolar vessels dilate, as they are no longer compressed by the difference between the intrabronchial and pleural pressure, and are easily distensible by virtue of their elasticity. These changes result in a considerable increase in the capacity in the blood vessels of the collapsed lung, the presence of which increase has been also demonstrated by injections and by the estimation of oxygen in cases of unilateral lung collapse due to an open pneumothorax.

It is to this hyperaemia of the collapsed lung that Sauerbruch attributes the dyspnoea of an uncompensated pneumothorax. The lung on the unaffected side is still able efficiently to aërate all the blood that passes through it, but as the result of the collapse of the other lung, and the associated increase of the size of the vessels, more than half the blood in the pulmonary system circulates through that lung and returns to the heart unoxygenated; there is a rapid increase of the carbonic oxide in the blood which, stimulating the respiratory centres, produces the dyspnoea.

It is to the genius of Mikulicz that we owe the first systematic attack on the physiological difficulty which beset the surgery of the thorax. At his suggestion Sauerbruch began in 1903 a series of experimental researches which have amplified our knowledge of

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the physiological problems concerned, and have given us a practical solution of them which has already enlarged the possibilities of surgery. The apparatus he set himself to design must, if it was to satisfy the requirements of the problem, provide not only for the prevention of collapse of the lung, but also for the continuance of active respiration and for the prevention of any serious displacement of the mediastinum upon one pleural cavity being freely opened. These conditions are satisfiable only if there is maintained a difference between the pressure of the air entering the trachea and the pressure on the surface of the lung, the latter being always negative in relation to the former. Such difference need never be great—approximately that of the elastic recoil of the lung, $7\frac{1}{2}$ to 9 mm. Hg—and it must be capable of being continuously and steadily maintained throughout the period during which the chest is open. It is obvious that these requirements can be fulfilled in two ways: First, the patient may be caused to breathe air of a tension greater than that of the atmosphere, so that when the chest is opened and the lung exposed to atmospheric pressure, this is less than that of the air the patient is breathing by an amount greater than the elastic recoil of the lung; and, secondly, while the patient is breathing air at atmospheric pressure, his body is exposed to air of pressure less than atmospheric, so that when the chest is opened there is no increase of pressure on the lung but the normal respiratory difference is maintained. It must be clearly understood that in the first-mentioned method (hyperatmospheric or *ueberdruck*) the increased pressure of the respired air is slight and is constant, there being no intention of inflating the lungs as in mechanical respiration, but rather the reverse of this, the object being simply to maintain the normal respiratory difference, so that normal active respiration may continue undisturbed. Sauerbruch experimented with both of these systems, and in 1904 completed a hypoatmospheric as well as a hyperatmospheric apparatus, with both of which he was able to carry out much successful experimental work. The former apparatus (*unterdruck Kammer*) is designed so that while the patient breathes air at atmospheric pressure, his chest, and after thoracotomy the surface of his lung, is exposed to a pressure less than that of the air. The latter apparatus (*ueberdruck Apparat*) allows of the patient breathing air greater than that of atmospheric pressure, while his body is exposed to normal atmospheric pressure.

While, however, Sauerbruch soon gave up his hyperatmospheric apparatus from preference of his hypoatmospheric chamber, Brauer⁴ also in 1904, and working independently of Sauerbruch, produced his model of a machine working on the hyperatmospheric system. This *ueberdruck Apparat* of Brauer was thus the first based on this system to come into general use.

A very brief description of the working principles of the Sauerbruch chamber and the Brauer machine must be given.

The hypotatmospheric chamber of Sauerbruch is an airtight room with an air lock for entrance and exit. The ventilation is regulated by a pump, but the air in the chamber is always maintained at a negative pressure equal to 7 to 9 mm. Hg below atmospheric. The operator and his assistants work in the chamber. The operating table is fixed against one wall, and opposite the head end there is an opening in the wall partially closed by a rubber sleeve. When the patient is placed on the table his head is passed out through the sleeve, which is then

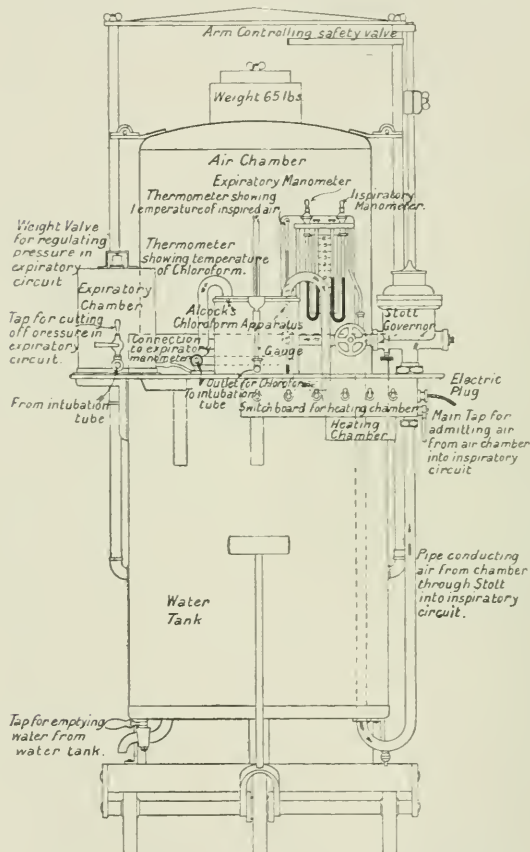


Fig. 3.—Scale drawing of front view of author's apparatus.

adjusted round the neck so as to be airtight. Thus the body of the patient is inside and is exposed to a negative pressure, while the head is outside in the normal atmosphere; the anaesthetist is also outside, and communication between those outside and those inside can be carried on by telephone. The legs and lower part of the patient's body are further enclosed in a rubber sack which communicates with the outer air, so as to exclude the greater part of the systemic circulation from the influence of the diminished atmospheric pressure. When the

thorax is opened under such conditions the movements of inspiration and expiration continue, and the lung on the exposed side remains in apposition to the chest wall. None of the phenomena of an uncompensated pneumothorax appear.

The Brauer hyperatmospheric apparatus works on the reverse principle—that is to say, that instead of a negative pressure of about 8 mm. Hg formed outside the exposed lung the lungs are kept charged with a positive pressure of the same amount. The apparatus consists of a motor (or pump worked by hand) which

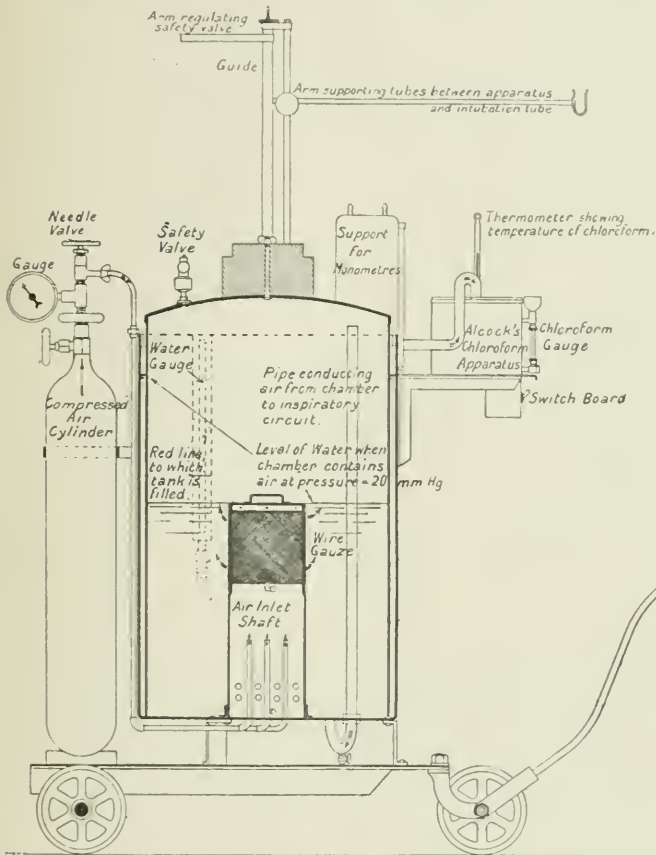


Fig. 4.—Scale drawing of sagittal section of author's apparatus.

forces air into a large bellows-like chamber expanding against springs; from this the air, at a pressure above that of the atmosphere, passes into a casket in which the head of the patient is enclosed. The casket has a glass top and two side openings fitted with rubber sleeves into which the anaesthetist inserts his hands and arms for the manipulation of the anaesthetic. The anaesthetic enters by a separate tube from a Roth-Dräger apparatus, and the pressure in the Roth-Dräger system and in the casket are equalized by a special device. The expired air

passes out through a tube fitted with a lever valve. This valve controls the pressure in the casket by permitting of escape of air when it exceeds the required pressure.

Since the introduction of these two types of differential pressure mechanisms there have been other various forms invented about which a few words must be said before a comparison of their merits can be made. The apparatus devised by Karewski⁶ resembles closely the Brauer *ueberdruck* and needs, therefore, no further mention. Willy Meyer⁶ has had constructed a big chamber whereby he can operate either with a positive or negative pressure. Two other types of hyperatmospheric apparatus, the Tiegel-Henle⁷ and the Lötsch,⁸ must be noticed because both have been brought forward with a view to putting on the market a simple, cheap, and portable mechanism²² for the prevention of uncompensated pneumothorax in intrathoracic surgery. The former of these introduces the air

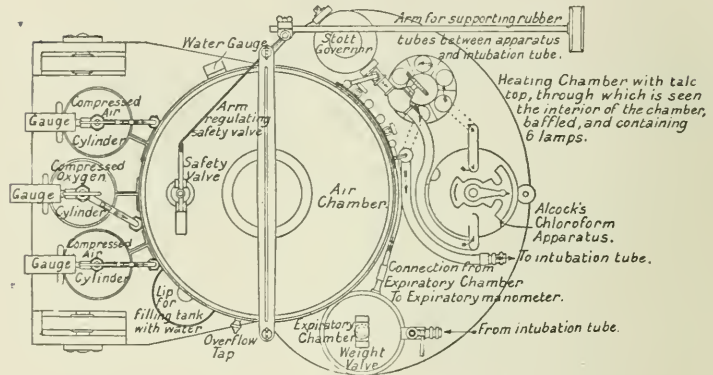


Fig. 5.—Scale drawing of author's apparatus, viewed from above.

by means of a tightly-fitting mask, the latter by mask or intubation tube. In both the expired air passes out through a column of water, and the pressure is regulated by the height of this column. There are thus two distinct types of differential pressure apparatus, the hypoatmospheric (*unterdruck*) and hyperatmospheric (*ueberdruck*). In the latter the compressed air reaches the lungs either by a casket, mask, or intubation tube.

COMPARISON OF THE HYPOATMOSPHERIC AND HYPER-ATMOSPHERIC SYSTEMS.

There is no doubt that the hypoatmospheric chamber reproduces the physiological state, when the chest wall is opened, more nearly than the hyperatmospheric apparatus, and Sauerbruch and Robinson⁹ and Haecker have demon-

* The Brauer with motor costs	...	about	£90
The Tiegel-Henle with 1 cylinder costs	about	£21	
" " with 2 cylinders costs	...	£26	
The Lötsch costs	...	about	£18

strated in their experimental pneumectomies on animals that there is less danger of the animal dying from effusion of serous fluid into the pleural cavity on the side of the operation when the experiment has been done in a hypoatmospheric chamber than when the hyperatmospheric system has been used. But on the other hand it has been shown from a series of experiments with the two types of apparatus¹⁰ that there is no material difference in the effect on the blood pressure or on the respirations during the operation. The great disadvantage of the hypoatmospheric apparatus is its size.

COMPARISON OF THE CASKET, THE MASK, AND THE INTUBATION TUBE.

It may at once be said that the mask is highly unsatisfactory, even when that form is used which has a vomit bag connected with it. It is difficult to make a mask to fit so well as to be airtight. It is most uncertain that all the vomit, should vomiting occur during the anaesthesia, will go into the special bag attached to the mask, and if

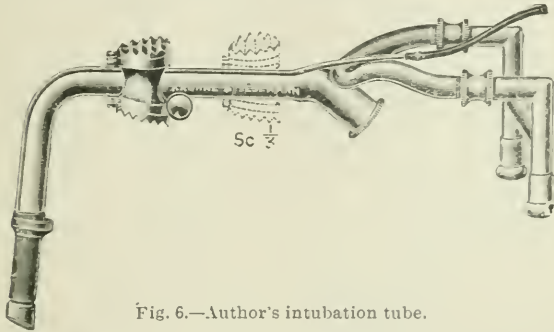


Fig. 6.—Author's intubation tube.

some of the vomit is inhaled, or if the tongue falls back, it is quite impossible to remedy these serious complications without removing the mask, and with it the increased pressure, whereas a constant maintenance of pressure is obviously essential.

The casket and the intubation tube are both satisfactory. In the casket, however, which must necessarily be large, the anaesthetic has to be introduced from a separate apparatus; the patient's neck is surrounded by a rubber band firmly applied to ensure against escape of air, and the anaesthetist must carry out all the necessary manoeuvres inside the casket with his hand surrounded by rubber; if he withdraws a hand to attend to the apparatus, the rubber sleeve is at once turned inside out by the pressure of the air in the casket, and has to be reinvaginated before he can again attend to the patient's head with that hand.

The objections raised against the intubation tube are that it may produce oedema of the glottis, is difficult to insert and restricts the air-way; unless considerable

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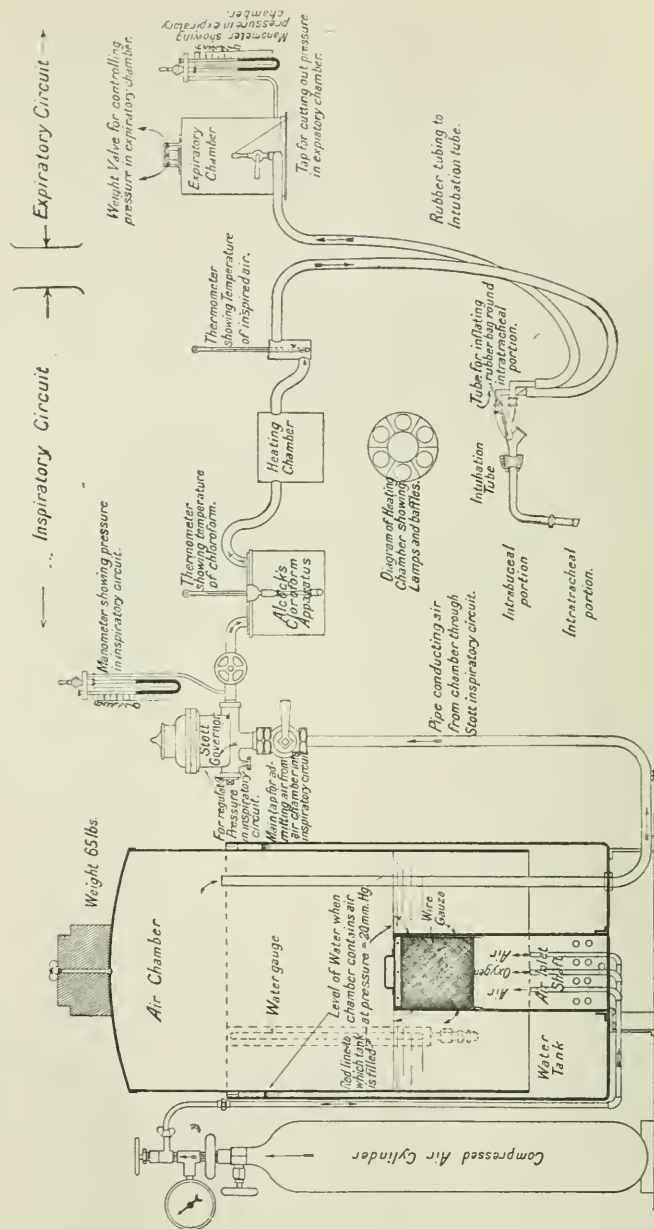


Fig. 7.—Scale diagrammatic drawing of author's apparatus.

irritation of the larynx is produced by careless intubation, there need be no fear of this complication, as has been shown by the extensive use of intubation by O'Dwyer and Kuhn, and the possibility of the use of the large instruments required for bronchoscopy and intrabronchial operations. With the finger on the glottis as a guide, the tube is easily inserted, and the constant stream of air amply compensates for the slight restriction of the air-way. The advantages of the intubation tube are considerable; the head is freed of all cumbersome enclosures with guarded apertures through which all the attention necessary for the administration of the anaesthetic, the holding up of the jaw, keeping forward of the tongue, removal of saliva and vomit from the mouth and pharynx, must be done; there is no danger of vomit entering the trachea, and once the tube is in position only one hand is required to keep it there. There is no constriction of the neck, which must tend to produce venous congestion of the brain and stormy respiration.

Before describing my own hyperatmospheric apparatus mention must be made of Meltzer's insufflation method.¹¹

Meltzer uses a long tube of about two-thirds the diameter of the trachea, which is passed down through the larynx to just above the bifurcation of the trachea. Air is pumped through this by bellows, and the returning air escapes between the tube and trachea. The method is said by those who have used it to answer its purpose, but Meltzer himself admits ignorance of the pressure of the air in the tube, and that, owing to the cyanosis and change in pulse-rate which develops, the lungs have to be allowed to collapse, and be then re-expanded once every few minutes. The method, then, would seem to be rather like mechanical respiration done with an irregular pump and a leaky apparatus.

My reasons for designing a new type of hyperatmospheric apparatus are as follows. The recognition of the necessity of being able to do intrathoracic operations without the constant anxiety of the risks of an uncompensated pneumothorax made me investigate the existing machines very fully. The *unterdruck* chamber of Sauerbruch needed so much space as to make it impracticable. Of the existing hyperatmospheric machines there were three different types to choose from—the Brauer; Tiegel-Henle; or Lötsch. Neither of these latter two suited my requirements, as in both of them, in my opinion, too great sacrifices have been made in order to secure cheapness and portability, and neither of them can be relied on for giving accurate working and a constant pressure throughout a long operation; in neither of them, therefore, can the maximum degree of security be said to be obtained. This does not imply that they cannot be used with considerable success, but it does suggest that by the inaccuracy and inconstancy of the pressure there is danger of increasing the shock of the operation. That the patient has often sufficient reserve to enable him to overcome remediable deficiencies of the instrument in no way justifies his being loaded with them in addition to the unavoidable necessities of the operation. In a department of surgery such as this,

where so much as to the conditions of successful treatment is as yet unknown. it seems to me most important that the highest standard of accuracy should be insisted upon with mere mechanical apparatus. and that no elaboration should be grudged which gives any possibility of increased safety.

Compared with these the Brauer machine is vastly superior: but there are certain objections to it. I have already suggested that the employment of a casket for the conveyance of the air at a positive pressure is not altogether satisfactory. The whole Brauer apparatus consists not of one but of two pieces of machinery, the Roth-Dräger chloroform machine with the intercommunicating pressure equilibrator. and the hyper-pressure part with its motor, air chamber, casket, and exit air valve, etc. As the air chamber is a large bellows working against the resistance of springs, the pressure of the air entering the casket must constantly vary, and the whole responsibility for maintaining uniformity of pressure in the casket rests on the respiratory valves. Lastly, the apparatus is very costly.

It seemed to me to be possible, working on a principle quite different from any of those already in use, to produce an apparatus by which absolute constancy in the flow and pressure of air could be combined with simplicity of working at a cost considerably lower at any rate than that of the Brauer type.

In designing such a machine, the following were the essentials which had to be determined on: the method of obtaining the air, the method of obtaining the pressure, the control of the pressure, the manner of conveying the air to the lungs, the administration of the anaesthetic.

For the reasons above given I decided on using an intubation tube in preference to the casket or mask, but the use of the intubation necessitates the exclusion of the mouth, nose, and pharynx from the air circulation, and it is therefore necessary that the air shall be moistened and warmed before passing into the trachea. Further, intubation necessitates an expiratory and inspiratory circuit, both under accurate and easily regulated pressure control. Neither rubber bags nor bellows expanding against the resistance of springs give constancy of pressure; the greater the distension of the rubber or the compression of the springs the greater the pressure, but an air chamber made on the principle of a gasholder with a suitably weighted inner cylinder will give an equal pressure, whatever the height of the cylinder. But the pressure of the air in the cylinder must always be as great as, and preferably greater than, the maximum pressure ever required, and some mechanism, therefore, is required to cut down the pressure to a constant quantity, yet allow of variation if required. This want is supplied by the Stott gas governor, which gives a constant pressure independently of the rate of flow; the pressure can be increased or decreased according as certain weights are increased or decreased. The supply of air is easily obtained from compressed-air

11. The relation of the air to the pressure. By THOMAS. February.
12. Acute Cardiac Failure. iii., No. 2.
13. The Humidity of the Air in the Lungs of Adults, to the Lungs. D. GILDEMEYER. Series B.
14. A note on the use of the Brauer machine. SILBERBERG.
15. The origin of the air in the lungs. SILBERBERG.
16. Ventricular failure. under chloroform. 18th. May.
17. The value of the air in the lungs. MORRISTON.
18. Observations on the action of the Heart Vol. 1.
19. The origin of the air in the lungs. By CHARLES.
20. The control of the air in the lungs. ELLIOTT.
21. The function of the air in the lungs. injections of alcohol. By C. H. H. (From *The British Medical Journal* 31st. 1912).
22. A Cardiac effect of adrenalin in chloroformed subjects. By A. G. LEVY. (From *The British Medical Journal* Sept. 14, 1912).

cylinders, and either air or oxygen, or a mixture of the two, can be given as required. As Alcock's chloroform apparatus is worked normally by driving air through it with bellows, and as it permits of accurate reading of the percentage of chloroform given according to the temperature of that fluid, it was possible, after a few minor alterations, to connect it up in the inspiratory circuit of my machine, and it has proved itself to be most satisfactory. Lastly, it was necessary that the various parts should be readily accessible for cleaning purposes, and so assembled that everything is within view and reach of the anaesthetist.

AUTHOR'S HYPERATMOSPHERIC APPARATUS.

The main features of the machine are an air chamber working on the principles of a gasholder and fed from compressed air and oxygen cylinders; the air in this chamber is at a greater pressure than that required in the bronchial tubes, but after it leaves the chamber passes through a governor and the pressure is there regulated to the required amount; it then passes through Alcock's chloroform box, then through a heating chamber, and so into the trachea by an intubation tube. The expired air leaves the trachea again by the exit pipe of the intubation tube and enters the expiratory chamber, where the pressure is again regulated by a weight valve.

Figs. 1 and 2 are woodcuts from photographs of the machine. Figs. 3, 4, 5 are scale drawings showing the various details. Fig. 6 is a woodcut of the intubation tube. And Fig. 7 illustrates the apparatus in diagrammatic form.

The whole apparatus rests on a steel triangular base with three wheels; the front wheel has a pivot action, and a handle is fixed to it by which the machine is moved about. The main air chamber consists of an inner and outer cylinder made of copper, tin lined. The outer cylinder or water tank is filled with water up to a mark shown on the water gauge, and the water serves both to control the air within the air chamber and to moisten the air as it enters the chamber. Attached to the base is the air inlet shaft, the lower part formed of tinned copper and perforated by holes round the bottom to admit free circulation of the water; the upper part consists of wire gauze; the top is closed by a cap, which is just below the surface of the water when the chamber contains air under pressure. Within this shaft open the three pipes from the compressed air and oxygen cylinders and the air as it escapes from these has to pass through the water and through the wire gauze.

The inner or air chamber rises and falls according to the volume of air inside it, and is kept steady by runners working on guides. The weight of this cylinder together with an extra weight of 65 lb. on the top of it keeps the air in the chamber at a pressure equal to 10 in. of water (approximately 20 mm. Hg). This cylinder is prevented from being lifted beyond a certain height by means of a valve which is opened automatically by a lever and allows the excess of air to escape. This valve can also be opened by hand when, should the chamber be full of air, oxygen is required; the replacement of air by oxygen when the chamber is full takes eight seconds and affects in no way the pressure in the inspiratory circuit. When the air chamber reaches its maximum capacity and before it reaches the minimum an electric contact is formed and a small buzzer rings.

To the back of the air chamber are attached three rings which hold two 40 ft. compressed-air cylinders and one 40 ft. compressed oxygen cylinder, which communicate by way of pressure gauges, needle valves, and flexible metal tubing, with the pipes entering into the bottom of the air chamber.

On the front of the air chamber is a tray which carries the

11. The relation of the air chamber to the governor. By THOMAS STOTT. February.
12. Acute Cardiac Failure. Part iii., No. 2.
13. The Humidity of the Air in the Lungs of Adults, to the Lungs of Infants. By D. GILDEA. Series B.
14. A note on the effect of the air chamber on the governor. By SILBERBERG.
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16. Ventricular failure under chloroform. 18th. May.
17. The value of the air chamber. By MORRISTON.
18. Observations on the effect of the air chamber. *Heart* Vol.
19. The origin of the air chamber. By CHARLES.
20. The control of the air chamber. By ELLIOTT.
21. The function of the air chamber in injections of alcohol. By CHARLES. (From *British Medical Journal* Sept. 14, 1912).
22. A Cardiac effect of adrenalin in chloroformed subjects. By A. G. LEVY. (From *The British Medical Journal* Sept. 14, 1912).

rest of the apparatus. An inch outlet pipe conducts the air from the air chamber into the governor. This pipe is U-shaped, and has a small tap at the bottom to allow the escape of any water which may collect in the pipe and the escape of condensed steam during cleaning. The main tap for connecting the air chamber with the inspiratory circuit is on this outlet pipe just below the governor. The governor is a half-inch Stott; the pressure is regulated by weights, and remains constant independently of the rate of flow. The pressure is shown by a manometer connected with the pipe immediately beyond the governor. The air is then conducted into Alcock's chloroform apparatus, which allows of accurate control of the percentage of chloroform used at various temperatures. The air charged with the required amount of chloroform passes next through a copper chamber containing six 16-candle power electric bulbs; this chamber is baffled so that the air must circulate round each lamp before it leaves. Each of the lamps has a separate switch; usually two lamps only are sufficient to produce the required temperature of about 85° F., but the additional number allows for the possibility of a fuse blowing or a broken filament. When the air leaves the heating chamber it is conducted past a thermometer, and then by a rubber tube to the intubation tube, which will be described presently.

In the expiratory circuit the air passes from the intubation tube into a metal box connected with a manometer and fitted with an expiratory valve which can be weighted to the required pressure. On the tube leading into this box there is a tap which can be opened if it is required suddenly to reduce the pressure.

The two manometers are arranged so that the ascending limbs are side by side; these and the thermometer are in a row, and the light from the electric lamps of the heating chamber fixed beneath the shelf shining through a talc disc illuminates them.

A movable arm fitted to one of the guides supports the rubber tubing between the apparatus and the patient.

The whole apparatus can be easily taken to pieces for cleaning.

The intubation tube consists of an intratracheal part fitted with a collar which rests on the glottis; a curved intrabuccal and an extrabuccal part. The intratracheal portion is surrounded by an airtight rubber sleeve which communicates with a very small pipe, through which it can be blown up. The intratracheal and buccal sections consist of a single tube ending externally in an open expansion, which is closed with a screw cap. The inlet and exit tubes which are joined up with the inspiratory and expiratory circuits enter the main tube just below the expansion.

Before the patient is intubated, the screw cap is disconnected and the patient breathes, and is given the anaesthetic through the opening of the expansion until the time when the pleura is about to be opened. The air is then turned on from the chamber, and as soon as it is flowing freely the screw cap is fixed, and the hyperatmospheric circuit thereby closed.

A movable gag is attached to the buccal portion of the intubation tube, so that the teeth can be made to hold the tube in position by putting a bandage round the jaw and head.

I have used this hyperatmospheric apparatus both on animals and men with complete success. The lungs are kept properly distended, the movements of inspiration and expiration continue unaltered, the pulse remains good as regards quality and frequency, the blood pressure is maintained, and there has been no trace of dyspnoea, even though the chest has been widely opened for one and a quarter hours in man and two hours in animals. During the operations oxygen has only occasionally been given. The details of the operations I hope to publish later.

My justification for publishing a detailed account of this apparatus is that it offers a certain combination of advantages not possessed by other hyperatmospheric machines. The pressure of the air remains constant, yet can be altered at will; the manometer in the inspiratory circuit shows only the slightest inspiratory and expiratory oscillations when the chest is opened, while the expiratory manometer shows a rise and fall of $\frac{1}{2}$ in. to 1 in. with each expiration and inspiration, according to the depth of the patient's respirations, and thus offers a very satisfactory guide to the condition of the patient and the depth of the anaesthesia. The pressure of air is regulated in both the inspiratory and expiratory circuits. The machine is extremely simple in its working, and the anaesthetist can reach and control every part of the apparatus with his right hand, the left being sufficient to steady the patient's head and the intubation tube. There are no motive forces such as motors, which may fail at any moment. The cost is about two-thirds that of the Brauer *ueberdruck*. It is capable of transport, and can be used in any theatre or operating room. Finally, its efficiency has been demonstrated by use.

I should like to take this opportunity of expressing my thanks to Mr. Rood for the trouble and care he has taken in the administration of anaesthetics for me with this apparatus.

Throughout I have profited greatly by the interest shown and the many valuable suggestions given me by Mr. Wilfred Trotter.

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11. The relative
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Sudden death under light chloroform anæsthesia. By
A. G. LEVY. (*A further communication.*)

(*From the Research Laboratories of the Medical School,
University College Hospital.*)

In a former communication (*Proc. Phys. Soc. Jan. 21, 1911*) I described some cases of sudden death in cats, which happened in the course of experiments under light chloroform anæsthesia, and which were due to fibrillation of the ventricles. I am now able to state that the deaths, which occur so frequently during the *induction* of chloroform anæsthesia, conform to this same type. Cessation of the heart's action, under these circumstances, occurs when the animal is obviously only imperfectly anæsthetised, and it is first indicated by a period of forced respiratory efforts, this being simply the physiological sequence of a rapid and complete circulatory failure. These respiratory efforts may, on occasion, be accompanied by loud expiratory groans, or by muscular spasm, tail spasm being characteristically frequent.

I have now observed eighteen cases of death of this nature, and also three cases of a similar collapse followed by recovery. In twelve instances the percentage of chloroform which was being administered was registered, and in none of them did it exceed 2%. On five occasions in which the percentage had been noted the heart was rapidly exposed immediately after death, and in each case I found the ventricles had ceased to beat but were exhibiting fine fibrillary contractions, more especially over the interventricular septum. The auricles continued to beat feebly for a long time, but in two hearts a short period of fibrillation in the right auricle was observed. The left auricle was always bright red in colour and contrasted with the purple hue of the right auricle.

The factor, in nearly all these cases, which preceded the onset of ventricular fibrillation was the withdrawal of the chloroform before a full degree of anæsthesia had been induced.

Illustrative case (1). 1% chloroform was administered by an *ad plenum* method for four minutes and the inhaler was then removed. As a consequence the cat immediately sneezed once and moved its head round gently, but there was no other movement. In twenty seconds from the time of taking the chloroform away the heart's action

was felt to cease abruptly, and after the usual period of forced respirations, the animal was found to be incapable of resuscitation. The cat was perfectly quiescent at the moment of cardiac failure, which was distinctly noted by digital palpation.

It frequently happened that some degree of struggling or sneezing immediately preceded death, and, more rarely, I have observed violent struggling to determine ventricular fibrillation even during the continued inhalation of a low percentage of vapour.

Illustrative case (2). 1% chloroform was given for seven and a half minutes. Spontaneous and violent struggling then ensued and terminated in a period of forced respirations with loud phonation. The heart was found to have ceased beating, but it resumed its action about thirty seconds later in the course of some small terminal respirations. This animal recovered permanently.

In a large number of instances the inhaler had been reapplied, on account of the animal showing signs of recovery, just previous to the heart's failure. The association of this act of reapplication with death is possibly nothing but a natural coincidence; at least I have at present no definite evidence to establish a causal relationship.

Cats are further very liable to die from this same cause when recovering from fully established anæsthesia, and I have met with six additional deaths in this category. (Ventricular fibrillation being sought for and confirmed by P.M. in two of these cases.)

By administering a vapour of 2%, or thereabouts, *in a perfectly continuous fashion*, cats may be anæsthetised without any risk, even in the event of violent struggling; at least that is my experience in over a hundred consecutive administrations.

HEART IRREGULARITIES, RESULTING FROM THE INHALATION OF LOW PERCENTAGES OF CHLOROFORM VAPOUR, AND THEIR RELATIONSHIP TO VENTRICULAR FIBRILLATION.

By A. GOODMAN LEVY AND THOMAS LEWIS.*

(From University College Hospital Medical School).

Introduction.

THE following research was undertaken with a view to the further elucidation of certain cardiac phenomena, originally observed by one of us in connection with the administration of low percentages of chloroform to cats, and described in the form of a preliminary communication to the Physiological Society.⁴ In this paper a peculiar form of blood pressure curve was described, which is characterised by rapid heart action, high or medium blood pressure, and certain fluctuations and irregularities which are made evident by reason of the inertia of the mercury column in the Ludwig's manometer. This peculiar form of curve was found to occur quite commonly under chloroform administered at a lower percentage strength than 1 per cent., or thereabouts; and it is necessary to emphasise the point that it was obtained with great frequency in animals which had not had a large initial dose of the anæsthetic, and that it was not seen when the animals were under the full influence of the chloroform; it may be added, in confirmation of its frequent incidence, that it was readily obtained in the five experiments which form the basis of the present paper.

The significance of this irregularity was deduced from its uniform appearance immediately before the occurrence of heart failure as a result of fibrillation of the ventricles, a condition which was shown to occur in certain isolated instances in the course of a series of experiments carried out in another investigation upon cats under the influence of chloroform. Certain other irregularities, characterised by a regular intermission of the heart beat, were also frequently observed and appeared to be conditioned by the administration of a somewhat less rarified proportion of vapour.

It was further demonstrated that fibrillation of the ventricles could be induced in a large proportion of cases by the intravenous injection, under light chloroform anæsthesia, of small doses of adrenalin chloride, a drug which does not have a like effect under full chloroform anæsthesia or under any other ordinary experimental conditions; and that, when the cardiac

* Working under the tenure of a Beit Memorial Research Fellowship.

tracing was regular in the period preceding the injection, it assumed a form of irregularity before the onset of fibrillation, which was apparently similar to that described above as occurring spontaneously.

These observations appeared to us of sufficient importance to call for an investigation which would reveal the precise nature of the several heart mechanisms present under light chloroform anæsthesia.

Method.

Cats were employed exclusively. They were anæsthetised with chloroform regulated in percentage terms by means of an apparatus already fully described by one of us.⁵ A definite and known percentage of chloroform was conveyed by means of a Brodie's pump, through an elastic bag which served to convert the stream from an intermittent into a continuous one, to a funnel completely covering the face of the animal.

A blood pressure curve was taken on a kymograph drum, Hürthle's manometer being employed, with half saturated sodium sulphate solution in the connecting apparatus. Electrocardiographic curves were also obtained from time to time throughout the same experiments. The lead was in each instance from right shoulder to left groin. Two electromagnetic signals working in a single circuit (one writing upon the kymograph drum, the other upon the photographic paper) allowed simultaneous index marks to be recorded, and permitted the identification of the same beats in the Hürthle curve and electrocardiogram.

Intravenous injections of adrenalin chloride, as supplied by Parke, Davies & Co., were employed in the experiments. The dose administered was $\frac{1}{4}$ to 1 minim of the 1 in 1,000 commercial solution, (0.016 to 0.065 milligrammes), this being diluted with twenty times its bulk of normal saline solution previous to injection into the saphenous vein.

The irregularities produced by light chloroform anæsthesia alone.

The sole reference which we have found to irregularities of the heart, of the forms we describe and in experiments on chloroform, is in a paper by McWilliam.⁸ This writer incidentally mentions irregularities, which apparently correspond to the premature beats and bigeminal pulse which are fully discussed in the following paragraphs.

The irregularities of the heart, seen under light chloroform anæsthesia alone, were of varied form; a number of these will be described, and the description will be simplified if the irregularities observed in a single and typical experiment receive detailed attention. Emphasis should nevertheless be laid upon the fact that, from experiment to experiment, the types of irregularity encountered were very constant in form. Irregularity of the heart occurred when the tension of chloroform vapour in the inspired air

varied between .5 and 1.5 per cent. Repeated observation showed a definite relationship between the mechanism of the heart and the degree of anæsthesia. Thus, any animal which had inhaled 0.5 per cent. vapour for a few minutes, presented irregularity of the heart's action, and this was often marked in its degree. Similar irregularities were observed with higher percentages, for example 0.8 to 1 per cent., but as a general rule the degree of irregularity was less marked. Continued inhalation of percentages exceeding 1.5 per cent, usually abolished all irregularity. Short inhalations of 2 per cent. invariably abolished it.

The experiment chosen to exemplify the effects of chloroform upon the undamaged heart is illustrated by the electrocardiograms in Fig. 4. The animal was anæsthetised with 2 per cent. vapour, and during the succeeding ten minutes the strength was reduced in steps to 1 per cent.. The heart beat perfectly regularly on this percentage for five minutes, when the strength was reduced to 0.5 per cent.. A minute or so later the electrocardiogram and Hürthle curve showed marked irregularity. An electrocardiogram taken at this stage presented a tachycardia at the rate of 280 per minute and of the type seen in Fig. 4, *VI*; the actual curve is not published. The second electrocardiogram was taken approximately five minutes after the inhalation of 0.5 per cent. vapour commenced and is shown in Fig. 4, *I*. The curve demonstrates a regular bigeminy of the heart, due to premature contractions, such as are obtained on excitation of the apical or left portions of the ventricular musculature. The sequential beats are represented by the usual summits, *P*, *R* and *T*, and each cycle of this form is followed by an anomalous complex of which the first deviation is in the apex-negative, the second in the base-negative direction. The sequential auricular contraction, (*P*) to which there is no ventricular response, falls with the anomalous complex and is readily identified in the curve.

The animal was next placed upon 1 per cent. vapour and after five minutes had elapsed, Fig. 4, *II* was obtained. The curve shows the regular occurrence of a premature ventricular contraction after each second normal or sequential cycle. It is to be noted that the type of anomalous ventricular complex has changed, but that it is still complicated by the sequential *P* summit which falls at or near its commencement. Fig. 4, *III* was obtained some five to six minutes later and subsequent to the reduction of the strength of vapour to 0.5 per cent.. The simultaneous Hürthle curve is shown in Fig. 1, and the corresponding beats in the two curves are numbered. A bigeminy is present in that part of the tracing covered by the signal marks, and it is brought about by premature ventricular contractions. The normal cycles (*P*, *R* and *T*) are followed by anomalous complexes and these are alternately of the types seen in Fig. 4, *I* and *II*.

A few minutes elapsed and the percentage was changed to 0.8 per cent. ; a little later the heart showed a trigeminy (Fig. 4, *IV*). Premature contractions are shown in this figure after each second normal cycle. The corresponding ventricular complexes are of a third type, and consist of first

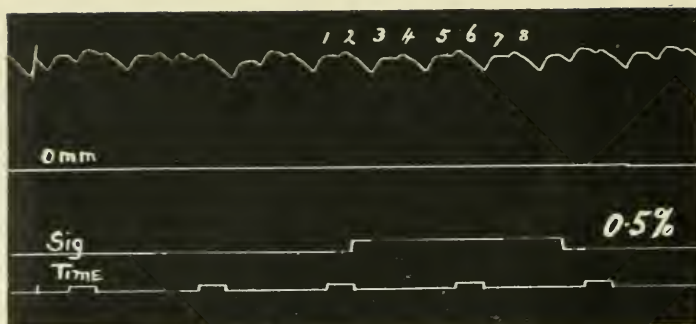


Fig. 1. A Hürthle manometer curve from the carotid of a cat under 0.5 per cent. chloroform vapour. The arterial curve shows an irregularity due to the presence of premature contractions. A portion of the curve, corresponding to the signal, has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, III. The time is in 1.8 sec..

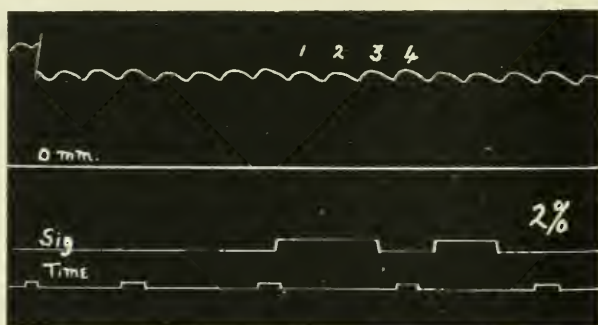


Fig. 2. A Hürthle manometer curve from the same animal, under 2 per cent. chloroform vapour. The arterial pulse curve is regular; the blood pressure has fallen. A portion of the curve corresponding to the signal has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, V. The time is in 1.8 sec..

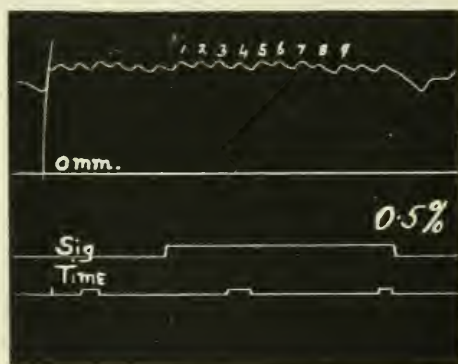


Fig. 3. A Hürthle manometer curve from the same animal, under 0.5 per cent. chloroform vapour. The arterial curve shows a number of rapid and almost regular beats, except towards the end where a pause occurs. Note the high blood pressure as compared to Fig. 2. A portion of the curve corresponding to the signal has its beats numbered; the same beats are numbered in the simultaneous electrocardiogram shown in Fig. 4, VI. The time is in 1.8 sec..

tall base-negative summits and secondly apex-negative summits; they conform in type to the anomalous complexes obtained upon stimulation of the basal or right portions of the ventricular musculature.

We need not concern ourselves with the accurate localisation of the origin of these beats; it is sufficient to emphasise the fact that each represents the origin of a ventricular contraction from a separate and fixed point or area, and that while in some curves the irregularity is due to new impulse formation from a single point or area (Fig. 4, *II*), in others two centres are active (Fig. 4, *III*).

The animal was placed upon 2 per cent. vapour and after the lapse of a few minutes the heart became perfectly and continuously regular. The mechanism is shown in Fig. 2 and 4, *V*, curves which were taken simultaneously. It is to be observed that the blood pressure had fallen somewhat with the rise in the percentage of vapour; the heart rate shown in the figure is 122 per minute. At the termination of this observation 0.5 per cent. was again administered and the simultaneous curves shown in Fig. 3 and 4, *VI* were obtained. The mechanism depicted in these figures, or a very similar mechanism, is extremely common upon the lighter percentages, and its analysis is aided by comparison with the other curves taken from the same animals. It consists of a rapid tachycardia of ventricular origin and is composed of beats which are placed at approximately regular intervals. The point of origin of the beats shown in Fig. 4, *VI* is variable and a comparison with Fig. 4, *I*, *II*, and *IV* shows that the new impulses are derived from areas which were previously active. Beats from three or more centres occur in haphazard sequence and follow each other at a rate of 232 per minute; no trace of auricular summits is to be found. It is probable that, with the establishment of the continuous tachycardia, the auricle is responding to ventricle and that the associated electric complexes approach the isoelectric state.

The Hürthle curve corresponding to this electrocardiogram is of peculiar interest, for it is, with the exception of the single long pause towards its termination, a regular and rapid pulse curve, in which the excursion of the several beats is approximately constant. Certainly the slight fluctuations seen are exaggerated when recorded by the mercury manometer, but the tracing as it appears in Fig. 3 might be readily mistaken, in the absence of other evidence, for that of a rapid and regular heart action of normal origin. The electrocardiogram, however, reveals the true nature of the condition; no single beat of sinus origin is present, but the mechanism is constituted by an ectopic rhythm generated in a number of ventricular foci. The importance of this conclusion is more evident when it is remembered that no *a priori* conclusions can be drawn in regard to the innervation of these new centres of impulse production. The approximate regularity of the tachycardia seems to be due to the appearance of a new contraction almost immediately at the cessation of the refractory period of the contraction which precedes it

Transitions between the simpler forms of irregularity shown in Fig. 4, *I-I V* and the tachycardia of Fig. 4, *VI* are common, and a single example which is taken from a separate experiment is shown in Fig. 5, the corresponding Hürthle curves as before being approximately regular. The auricular representatives are easily distinguished throughout the whole of this strip, but only a solitary normal cycle (*P*, *R* and *T*) is present. The premature contractions are coming from a number of separate ventricular foci.

A very curious type of tachycardia has been seen on several occasions and is illustrated by Fig. 6. It is a perfectly regular tachycardia generated from two separate ventricular foci, and the beats from one and the other focus occur alternately and follow each other at a rate of 312 per minute. In the corresponding Hürthle curves, the presence of two types of beat is recognisable only upon the very closest examination. The ventricular complexes of the beats follow each other so rapidly that each appears to start before the completion of the preceding one, and as a result the quick opening phases, some of which are directed upwards and some of which are directed downwards, do not start from the same abscissa. The explanation of the absence of return of the string to the isoelectric position before the occurrence of each new contraction is not apparent.

The effect of small doses of adrenalin upon the heart under the influence of low tensions of chloroform vapour.

In the first instance, it will be convenient to describe the result of injecting adrenalin, when the cat is under the full influence of chloroform; the sequence of events is similar to that described in the following typical experiment. An animal was anaesthetised with chloroform of 2 per cent. strength, which was gradually reduced to 1.5 per cent.. Thirty-one minutes from the commencement of the experiment, the anaesthesia was well established at this percentage; a faint corneal reflex was present, and the heart beat regularly at a rate of 160 per minute; the mean blood pressure was low, namely, 63 mm. Hg.. Under these conditions, 0.065 milligrammes of adrenalin chloride were injected intravenously. Approximately twenty seconds after the injection irregularities commenced to show themselves in the electrocardiogram, the first premature beat being an accompaniment of the rise of blood pressure, which had at this point reached a height of 90 mm.. The premature ventricular contractions became more numerous as the pressure rose to 100 mm. and irregular mechanisms were encountered, which were similar to those previously described as occurring under the influence of light chloroform anaesthesia alone, (cp. Fig. 4, *I I*, and Fig. 5*). The

*The similar mechanisms described by Kahn³ were obtained in dogs deeply anaesthetised by a mixture of chloroform and ether. (Communication by letter).

blood pressure having reached a maximum of 120 mm., the heart, 64 seconds from the time of injection, settled down into a regular tachycardia from a single point, probably located in the left or apical portions of the ventricular musculature. One minute later, the blood pressure had fallen to 105 mm., and the heart was beating at a regular rate of 210 per minute, and its mechanism was normal.

When the animal is under low percentages of chloroform vapour, the injection of adrenalin is followed by results which are far more profound than those obtained in animals under the higher percentages. It may be that, when the injection is administered, the heart is presenting the irregularities commonly found under light anæsthesia, or it may be that it is beating regularly; but independently of its initial condition, and provided that the anæsthesia is light, the injection of 0.016 milligrammes or more of adrenalin chloride is followed by the appearance of multiple premature ventricular contractions, and finally the disorder of the mechanism culminates in fibrillation. This sequence of events is exemplified in the following description of the result of a second injection of adrenalin into the same animal, which was the subject of the experiment already recorded.

At the conclusion of the previous observation, the percentage was reduced to 0.5 per cent., and the injection of 0.065 milligrammes of adrenalin chloride was given fourteen minutes later. At the moment of injection the blood pressure was 130 mm. Hg., and the pulse rate 277 per minute, the mechanism of the heart beat being one of alternate beats generated in two separate ventricular foci, and the curves being similar to those shown in Fig. 6. This mechanism continued for seventeen seconds, and at the end of this time, the blood pressure measured 145 mm.. The mechanism of the heart then suddenly changed to one in which beats from a number of foci followed each other at a rate of 230 per minute, and this continued for a period of two seconds, the blood pressure rising abruptly at the same time to 180 mm.. At the conclusion of this period, the ventricles fibrillated.

In another instance in which the same quantity of adrenalin was injected under 0.5 per cent. chloroform, the heart at first beat quite regularly at a rate of 120 per minute, it then passed suddenly into a condition of irregular tachycardia, generated in multiple ventricular foci. This lasted for seventeen seconds and terminated in ventricular fibrillation. The latter part of the tachycardia and its passage into fibrillation is shown in Fig. 7.

As a rule the onset of ventricular fibrillation terminates the experiment, for the ventricles fail to recover from it; but complete recovery from fibrillation lasting three seconds has been seen in one animal. From a number of kymograph tracings in our possession, it is obvious that permanent recovery from well established fibrillation is a rare event in the cat. In the above mentioned instance, a further injection under 0.5 per cent. vapour caused fibrillation, from which there was a temporary recovery, lasting some six seconds, the heart passing again into fibrillation, which, on this occasion, persisted.

When there is recovery from fibrillation, the mechanism at the offset is similar to that seen at the onset; tachycardias of the several forms described are present. The normal sequence is re-established with the administration of higher percentages of chloroform.

Briefly, the irregularities produced by adrenalin in small doses, when the animal is under *high* percentages of chloroform, are of the same nature as the irregularities produced by low percentages of chloroform alone; whilst small doses of adrenalin in the presence of low tensions of chloroform ultimately produce the highest grade of disorder, which is known to effect the ventricle, namely, fibrillation.

The electrocardiographic curve corresponding to ventricular fibrillation has been incidentally referred to by Kahn² and also by Jolly and Ritchie.¹ When the ventricle first passes into so-called fibrillation, its tone is increased, the visible movements are very active, and the oscillations are almost, but not quite, regular at a rate of 400 to 800 per minute. During this stage, a series of conspicuous and slow undulations usually occurs in the record, and this is well seen in Fig. 8. The curve as a whole shows a waxing and waning in the excursion of the oscillations at a rate of about 50-60 cycles per minute. The slow undulations are apparently associated with waves of tone change in the muscle, probably similar to the peristaltic waves spoken of by McWilliam.⁷ This stage of fibrillation, from which recovery is evidently possible in the cat, gradually gives place to a second condition in which the ventricle becomes more distended and in which the slow undulations are absent or inconspicuous, and in which the rapid oscillations occur at a slower rate (300-360 per minute) and in a far more irregular fashion. This mechanism, from which recovery has not been observed, is shown in Fig. 9. Similar appearances were seen by one of us in a series of experiments upon obstruction of the coronary arteries, experiments which frequently terminate in ventricular fibrillation, and similar changes have been noted also where fibrillation has been induced by faradic stimulation. The change from one type of fibrillation curve to the other, therefore, is not confined to experiments under chloroform and adrenalin; further, by whichever of these means fibrillation is induced, it is preceded by tachycardia of ventricular origin.

DISCUSSION.

The hearts of cats, influenced by low tensions of chloroform vapour alone, or by adrenalin in the presence of high percentages of chloroform, exhibit disorders of mechanism of a very definite type. So far as our observations are concerned, the disturbances result purely from the production of new impulses in the ventricles. The nature of these impulses has been fully discussed by one of us in a recent publication,⁶ and the beats have been termed *heterogenetic* on account of the short pauses which precede them and because they do not appear to stand as essential integers in a rhythmic

series of beats. Interpreting the events, in the light of the hypothesis put forward, we may state that the irregularities resulting from chloroform administration, are the outcome of an ever increasing tendency towards the production of heterogenetic beats ; at first isolated and generated from a single foci, these beats subsequently become more numerous, and arise from several foci ; eventually the rhythm of the ventricle is entirely dominated by impulses of this nature, and immediately prior to the onset of the final inco-ordination in the adrenalin experiments, a number of foci are active. Final fibrillation can only be regarded as a further step in the train of events ; it is believed that it results from the activity of a number of new foci of pathological or heterogenetic impulse formation, and that a grade of inco-ordination is produced in the ventricular musculature, such as precludes the output of blood from the organ and brings the circulation to a speedy standstill.

Chloroform in low percentages produces an enhanced irritability of the ventricle, a condition in which there is a widespread discharge of pathological impulses from the musculature, or a condition in which there is a tendency to such discharges. A further interference, such as is brought about by adrenalin injection, is followed by the highest grade of ventricular disorder, *i.e.* fibrillation, and death results. The method in which the adrenalin acts on hearts, whether, for instance, by directly affecting the heart muscle or indirectly through its pressor action, is not a matter which concerns the present investigation, and cannot be discussed here. It is apparent, however, from the foregoing considerations that the heart under low tensions of chloroform vapour may be in a condition which is the immediate antecedent of ventricular fibrillation. This is obviously a matter of important clinical interest in relation to the causation of sudden death under chloroform anæsthesia.

The experiments are also of interest in that they help to elucidate the pathology of ventricular fibrillation. They appear to confirm the supposition that this disorder of the musculature results from the generation of heterogenetic or pathological impulses from a number of foci in the chamber itself.

The tachycardias observed under low tension chloroform vapour are of importance ; they are of purely ventricular origin, and cannot be ascribed to any central nervous disturbance. They illustrate the value of the electrocardiographic method, for in the absence of records of this nature, the heart mechanism might be and probably has been mistaken for a normal or sequential one ; and the acceleration of heart rate might be readily ascribed to altered innervation. It is necessary to emphasise the danger of serious fallacy when conclusions are drawn from sudden accelerations or retardations of pulse rate as recorded by a mercurial or membrane manometer. Mechanical records of this kind fail to provide the experimenter with an analysis of the heart mechanism and the changes in rate are too often interpreted as the result of central nerve influences.

CONCLUSIONS.

1. Low tensions of chloroform vapour, administered to cats, produce high grades of irregularity of the heart. The irregularities are due to the production of new impulses in the ventricular musculature.

2. Small intravenous injections of adrenalin chloride produce, under high percentages of chloroform vapour, a condition of irritability in the ventricle, which is similar to that observed to result from low percentages of chloroform alone.

3. Low tensions of chloroform administered to cats together with small intravenous injections of adrenalin chloride ultimately produce the highest grade of ventricular disorder, *i.e.*, ventricular fibrillation.

4. Ventricular fibrillation is the result of the origin of impulses at a number of separate foci in the ventricular musculature.

5. The irregular and rapid heart beat referred to in the introduction of this paper as a common accompaniment of the administration of low percentages of chloroform, and as a precursor of isolated instances of death from ventricular fibrillation in cats, is in fact a transitional stage towards ventricular fibrillation.

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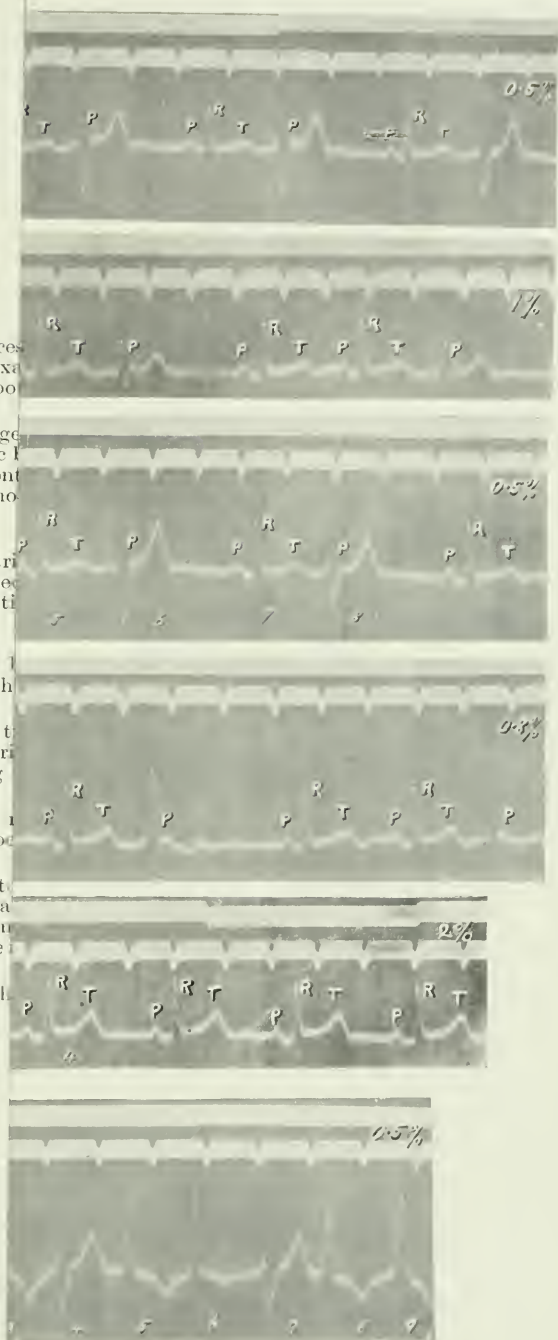


FIG. 4.

Fig. 4. λ . 3. A succession of electrocardiograms from a single animal; they are published as characteristic examples of the action of chloroform upon the cat's heart. The percentages of chloroform vapour are marked on the right hand corners of the respective figures.

I. A bigeminy resulting from the presence of premature ventricular contractions. The rhythmic beats are marked *P*, *R* and *T*, (*P*=auricle, *R* and *T*=ventricle). The premature contractions are complicated by the presence of the sequential *P*'s, which fall on the shoulders of the ascending portions of the corresponding ventricular complexes.

II. A trigeminy resulting from premature ventricular contractions of a different type. The electric curves corresponding to the premature contractions are complicated by the sequential auricular contractions (*P*), which fall in the centres of the corresponding complexes.

III. A bigeminy resulting from premature contractions, which are alternately of the forms shown in *I* and *II*. A simultaneous Hürthle curve is shown in Fig. 1.

IV. A trigeminy resulting from premature contractions of a third type. The sequential auricles are clearly shown upon the downstrokes of the electric complexes corresponding to the premature contractions.

V. The regular mechanism shown under 2 per cent. vapour. The rate of heart beats is 122 per minute. The corresponding Hürthle curve is shown in Fig. 2.

VI. A tachycardia produced by 0.5 per cent. vapour, and consisting of a complex mixture of beats of the types shown in *I*, *II* and *IV*. The tachycardia is due to the formation of impulses in several foci of the ventricular musculature. The corresponding Hürthle curve is shown in Fig. 3.

In all the curves, the upper line shows the signal, the second line fifths of seconds.

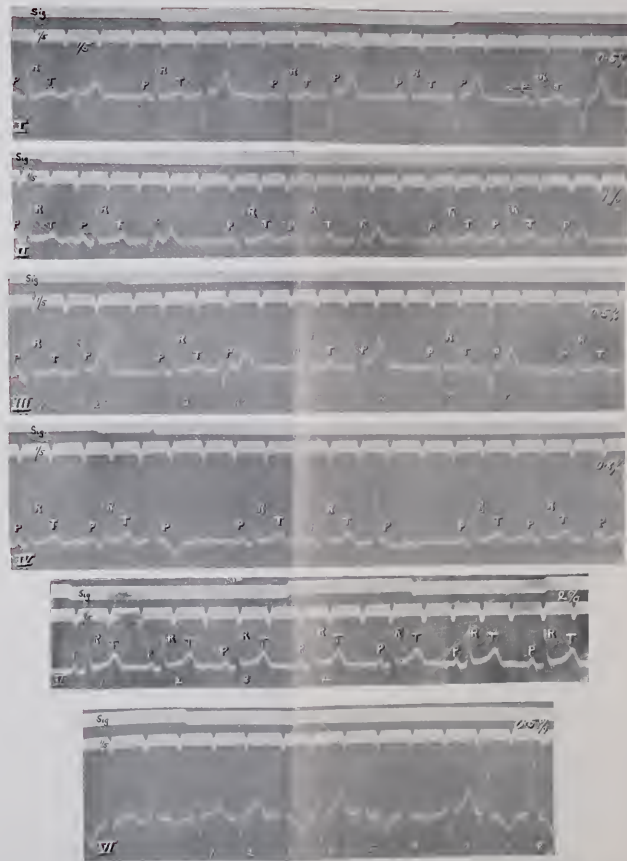


FIG. 4.

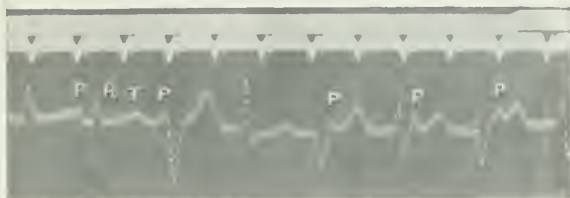


FIG. 5.



FIG. 6

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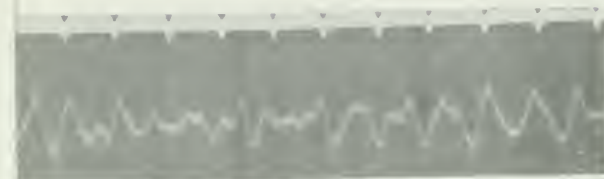


FIG. 9.

Fig. 5 $\times \frac{2}{3}$. An electrocardiogram from a cat under 0.5 per cent. vapour, showing marked irregularity resulting from premature ventricular contractions. Only a single normal or sequential beat is present; it is marked *P*, *R* and *T*, and lies in the centre of the figure. The rhythmic auricular contractions may be identified throughout the whole curve. They are marked *P*.

Fig. 6 $\times \frac{2}{3}$. Shows a tachycardia composed of premature contractions alternately generated in separate foci. This mechanism was present when the animal was upon 0.5 per cent. vapour

Fig. 7 $\times \frac{2}{3}$. The transition from a complex tachycardia to ventricular fibrillation. The tachycardia was induced by the injection of adrenalin under 0.5 per cent chloroform, the heart being originally regular.

Fig. 8 and 9 $\times \frac{2}{3}$. Two electrocardiograms from a single animal; exemplifying the appearance of ventricular fibrillation, resulting from the injection of a small dose of adrenalin; shortly after its onset (Fig. 8) and a few minutes later (Fig. 9). In Fig. 8 the oscillations follow each other at a rate of approximately 780 per minute; a series of slow undulations is present in this curve; (it is at this stage that the heart is contracted and in very active movement). In Fig. 9 the oscillations occur at a much slower rate, approximately half the preceding rate, and the slow undulations are no longer present, (it is at this stage that the heart is markedly dilated, and that the movements consist of feeble flickerings on the surface).



FIG. 5



FIG. 6



FIG. 7.



FIG. 8



FIG. 9.

PREMATURE CONTRACTIONS ARISING IN THE JUNCTIONAL TISSUES

By THOMAS LEWIS¹

(From University College Hospital Medical School)

With Plate 1

PREMATURE contractions arising in the junctional tissues are comparatively rare in patients. Instances in which beats are supposed to have arisen in the neighbourhood of the auriculo-ventricular node have been reported by Mackenzie (8) and Hering and Rihl (4), and the localization in these examples was arrived at by means of polygraphic curves. A solitary clinical example of the electro-cardiographic curves of nodal beats was given in an earlier publication (6); the case was one in which paroxysms of tachycardia occurred, and in which auricle and ventricle beat simultaneously. James and Williams (5), in their general paper on electro-cardiograms, have published a figure which is probably from a case of premature beats arising in the node. The localization of nodal beats in the past has depended in the main upon the recognition of simultaneous and premature contraction in both auricle and ventricle, the instants of onset of contraction in one or other chamber being fixed by means of polygraphic curves. Similar heart mechanisms have been observed in experiment, and have been published by Lohmann (7), Hering (2), Rothberger and Winterberg (9) and myself (6). The mechanism in premature beats of the form considered is not entirely clear, and chiefly on account of the difficulty of ascertaining the rates of transmission through the node and bundle in one or other direction. Recent observations by Hering (3) seem to show that the chief delay in transmission occurs in the node itself, and consequently that if (*a*) the intervals between onsets of auricular and ventricular systole are reduced in the premature beats, or if (*b*) the two systoles are quite simultaneous, or if (*c*) the ventricular systole slightly precedes the auricular, then the premature impulse has arisen in the node or its immediate neighbourhood and has given rise to coincident or partially coincident contractions in the upper and lower chambers.

At the present time, chief interest centres in the electro-cardiographic curves associated with heart contractions of this form. If a contraction impulse starts in the node or in the main bundle, it travels to the ventricle through the normal paths, and consequently the ventricular contraction may be

¹ Working under the tenure of a Beit Memorial Research Fellowship.

expected to be of normal type. The electric complex corresponding to it should have approximately the form given by the rhythmic beats in the same case. When the ventricle contracts prematurely and the electric complex corresponding to it is of normal outline, or more correctly when it has an outline similar to that of the ventricular complex of the rhythmic beats in the same case, the impulse which gives rise to it is of supraventricular origin; that is to say, it starts in the auricle, in the auriculo-ventricular node, or in the bundle up to the point of its division. The form of the premature ventricular complex consequently gives an immediate clue to the chamber or tissue in which the impulse has arisen.

The accompanying curves were taken from a case of aortic regurgitation. Fig. 1 shows electro-cardiograms from the three usual leads, right arm to left arm, right arm to left leg, and left arm to left leg; each strip presents a single premature contraction of the ventricle, and in each instance the ventricular complex of the premature contraction is similar in form to the complexes corresponding to rhythmic beats. It may consequently be concluded that *the impulse giving rise to these premature contractions originated in a supraventricular focus.*

The second point to be noted in the curves is the absence of disturbance of the auricular rhythm. The pause following each premature beat is always fully 'compensatory',² and in the majority of the curves the sequential *P* summit, i. e. the auricular contraction which fails to yield a ventricular response because its impulse falls in the refractory period of the ventricle, is plainly visible. For example, it is seen in the second strip of Fig. 1, and precedes the small upstroke *R* of the premature ventricular complex. The ventricle has not responded to this auricular contraction, for the corresponding *P-R* interval is curtailed. In the third lead the commencing upstroke of *P* is seen, and is succeeded almost immediately by the small upstroke *R* of the premature ventricular complex. In this instance the *P-R* interval is reduced from the normal length, 0.16 sec., to 0.04 sec. In the first lead the sequential auricular contraction falls with *R* of the premature ventricular complex and is not visible. The conclusion from these findings, namely, the absence of disturbance of auricular rhythm and the absence of relationship between the time of onset of auricular and ventricular contractions, is clear. The premature contractions have had little or no influence upon the sequential auricular contraction. *Therefore they have arisen at some point below the main mass of auricular musculature.*

The two main conclusions may be combined in the statement that the point at which the premature contractions originate lies between auricle and ventricle, and either in the auriculo-ventricular node or in the bundle before its division.

Now the accumulated evidence goes to show that a premature impulse arising in the node will give rise to a premature contraction in both auricle and ventricle, while a single premature contraction arising in the ventricle rarely, if

² Sometimes the pause is slightly increased beyond this, as a result of an accompanying sinus slowing.

ever, passes back to the auricle. There is always some obstruction to the occurrence of a single retrograde beat, and it appears as if this obstruction is mainly in the auriculo-ventricular node. When a supraventricular impulse fails to affect the sequence of auricular contractions, as in this case, we are tempted to conclude that such an impulse has arisen below the node itself, that is to say in the main bundle. In the present instance the conclusion would be more justifiable were it not for the curious relationships of the commencements of auricular and ventricular systoles. The sequential auricular complex *P* usually precedes the commencement of the premature ventricular complex (second and third leads of Fig. 1), and it may be held that the auricle has failed to respond because the impulse travelling upwards has encountered an auricular impulse travelling downwards; or that (in the first lead) the auricle is in contraction and its muscle is refractory when the impulse reaches it. In no observed instance, in this patient, has the auricular contraction fallen so far ahead of the upstroke of *R* that the last possibility can be absolutely excluded. But it has fallen sufficiently ahead of it (Fig. 2) to render it probable that the point at which the impulse of the premature contraction arises lies at some distance from the auricle.

These considerations make it probable that we are dealing with an instance of premature beats arising in the auriculo-ventricular bundle rather than in the node itself.

Note. The type of ventricular contraction found in this case corresponds to that described as characteristic of hypertrophy of the left ventricle, a fact in accordance with the presence of aortic regurgitation. In Fig. 1, lead *I*, *R* is increased, in lead *III* *R* is markedly diminished and *S* greatly exaggerated. (See Einthoven (1).)

Summary.

1. An instance of premature contractions arising in the junctional tissues is described. The impulses probably originated in the auriculo-ventricular bundle.
2. Premature contractions arising in the junctional tissues do not necessarily affect the auricular rhythm.

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EXPLANATION OF FIGURES.

FIG. 1. ($\times \frac{5}{7.5}$.) Three electro-cardiograms from a case of aortic disease. Each strip in this figure shows a single premature contraction. *I*, lead from right arm to left arm; *II*, lead from right arm to left leg; *III*, lead from left arm to left leg. The premature ventricular complex closely resembles the complex of the regular beats in each lead. The auricular beats (*P*) occur at regular intervals throughout the curves.

FIG. 2. ($\times \frac{5}{7.5}$.) Lead from right arm to left arm in the same case. The sequential auricular contraction (*P*) falls in the centre of the premature ventricular complex.

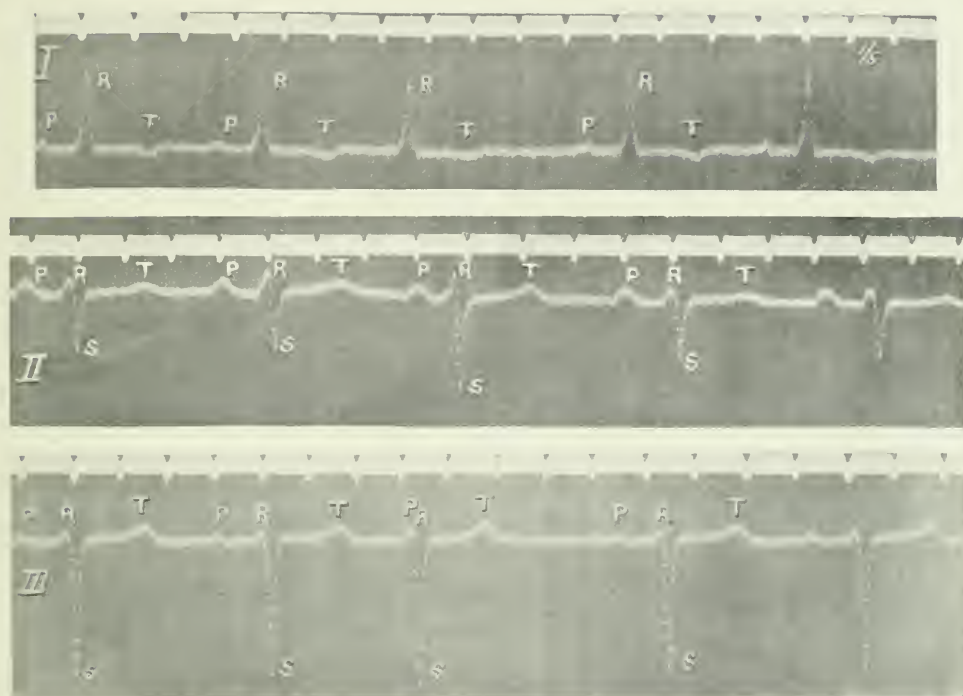


FIG. 1



FIG. 2

PAROXYSMAL TACHYCARDIA ACCOMPANIED BY THE VENTRICULAR FORM OF VENOUS PULSE

BY THOMAS LEWIS¹ AND M. D. SILBERBERG

(From University College Hospital Medical School)

With Plate 2

A HOUSEWIFE, aged 23, was admitted to University College Hospital on April 10, 1911, complaining of attacks of palpitation. The observations made upon her are of importance in that they help in elucidating an obscure form of paroxysmal tachycardia.

Family history. Her mother died of phthisis at the age of 38. Her father died of 'heart disease'. One sister died of phthisis, one from diphtheria; there were three brothers living, one had had acute rheumatism, two were healthy. She had a baby 14 days old. The husband was healthy.

Personal history. She was in domestic service before marriage (eighteen months ago), but gave it up because she could not manage to climb stairs, as it brought on shortness of breath. The bowels had been regular, she slept well, and her appetite was good. Menstruation was regular before pregnancy. There had been no miscarriages.

Previous illness. She was not strong as a child, suffering from enlarged tonsils, sore throats and rheumatic fever; the first attack of fever was at 8 years of age, the next attack at the age of 11 years. She was treated at Great Ormond Street Hospital on both occasions.

Present illness. She stated that she had suffered from attacks of palpitation since she was 14 years of age. From 14 to 16 they were infrequent, occurring about once in six months. At 17 years of age they appeared more frequently, and generally just before the onset or just at the cessation of the menstrual periods. After this they became less frequent, occurring about once in nine months, till four months ago. At this time she was five months pregnant and attacks were very frequent; she experienced as many as four or five attacks a week. She said that excitement or slight exertion might bring on an attack. There was no warning of the attack, except perhaps a lump in the throat; the onset was abrupt and often unexpected. She felt suddenly helpless and faint, but did not fall; she could not lie down, preferring to sit or stand. There was difficulty in speaking because of a choking sensation in the throat, which she said was due to the rapid throbbing in the vessels of the neck. She felt her heart to be palpitating and said that during the progress of the attack her heart felt as if it were moving to the left and growing bigger. When her heart seemed as if it were right round under the armpit, she had a slight dull aching pain in this situation. At these times she had great difficulty in breathing and thought she was taking her last breath and about to die. She said she felt as if she could not get her breath out of her chest because her heart was beating so quickly. She could walk about in the attacks, and often preferred to do so because

¹ Working under the tenure of a Beit Memorial Research Fellowship.

she found that the palpitation gradually quietened down; if she lay down, she was often more helpless and weaker than when sitting; the palpitation increased and the breathing was more distressed. Although she preferred to walk, and could do so without assistance, she was quite incapable of performing even the slightest exertion (climbing one stair, &c.). The attacks varied in duration from ten minutes to a day and a half. In practically all the attacks she brought up a lot of wind, and with this some green vomit. Vomiting nearly always stopped the attack. She said that, if the vomiting did not occur spontaneously, she induced retching by 'sticking her finger down her throat', and that this was often effectual. She had observed that an attack might start as a result of turning on to either side when in bed, or as a result of stooping suddenly; some of them had waked her from sleep. When she was younger, a hard day's work was frequently followed by an attack during the next day. While she was pregnant, the attacks were most frequent and occurred daily. Since the child was born (fourteen days previously) she had had three attacks, two attacks lasting a day and one short one of about an hour's duration. At the termination of the attack she felt a hot flush all over, sweated freely and was momentarily giddy. She said that the heart seemed to stop still for a moment and then resumed its ordinary beating, or she might feel three or four big thumps and then the ordinary regular beat again. The termination brought a marked sense of relief, and she was at once capable of setting about her household duties as if nothing had happened. Afterwards people told her that her eyes were puffy.

Physical examination, April 28, 1911. She was a fairly well-nourished woman and had a somewhat pallid complexion. Temperature 97-98°. Pulse 72 and regular. The arteries showed no thickening and the pulse was of good volume.

The heart's dullness lay $\frac{3}{4}$ and $4\frac{1}{4}$ inches to right and left of the mid-sternal line when she was supine. The impulse was palpable in the fifth space. A diastolic thrill was palpable over the apex. At the apex, a systolic murmur and a well-marked diastolic murmur, not quite filling the whole of diastole, were heard. The second sound was well marked. The mitral systolic was conducted into the axilla, the diastolic was conducted only between apex and third interspace. At the base, the second pulmonary sound was accentuated and reduplicated, and the aortic sounds were clear.

Occasional sibilant rhonchi were heard over the right apex, but no crepitations. There was no impairment of the percussion note. There were some signs of emphysema. The liver was just palpable.

Notes of the attacks. Attacks of tachycardia were observed on several occasions. There was a paroxysm on April 13 (three days after admission), which lasted for more than fifteen hours; during it venous curves were obtained. A shorter attack, of about two hours' duration, occurred on the 18th, and on the 23rd she had an attack lasting eight hours, during which electro-cardiographic curves were obtained. On the 27th there was a brief attack in the night; on the 29th she woke 'with palpitation'. The paroxysm lasted twelve hours and, as in previous experiences, ended quite suddenly. Speedy relief from symptoms always accompanied the offsets.

During the long paroxysm of April 13, and towards its termination, examination showed the condition to be critical. The patient was very pallid and cyanosed, and presented a trace of jaundice. The breathing was very distressed; respirations were at the rate of 40-50 per minute. The pulse varied from 180 to 200 per minute. The right and left margin of the heart's dullness lay $2\frac{1}{2}$ inches to the right of the mid-sternal line and in the mid-axillary line respectively. The liver reached to the umbilicus, was hard, tender and pulsating. A number of remedies were tried without avail; for example, injections of digalen (10 minims) and strophanthine (1/250 grain). Ice packs were applied to the chest and vagal compression was repeatedly tried, but the attack continued until several hours later it terminated with the onset of vomiting.

Polygraphic Curves.

The venous curves taken during the slow heart periods show the mechanism to be sequential; the $a-c$ interval is a full $1/5$ second in Fig. 1. During the paroxysms the ventricular form of venous pulse appeared (Fig. 2) and accompanied a regular radial pulsation at from 180 to 200 per minute. The jugular

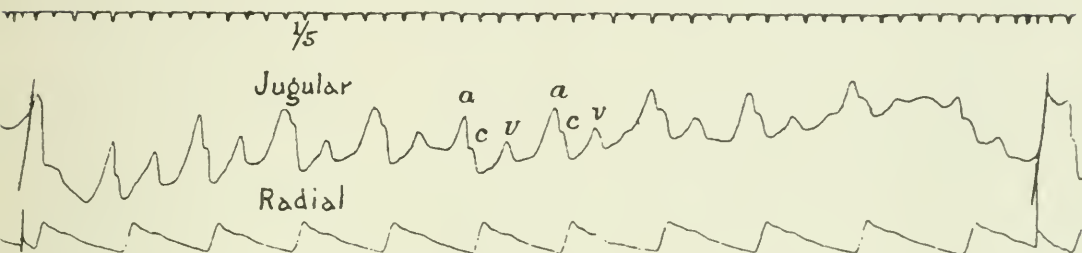


FIG. 1. A polygraphic curve taken while the heart action was normal in sequence and rate. Each radial cycle is accompanied by a , c , and v waves in the corresponding jugular cycle. The rate is 190 per minute.

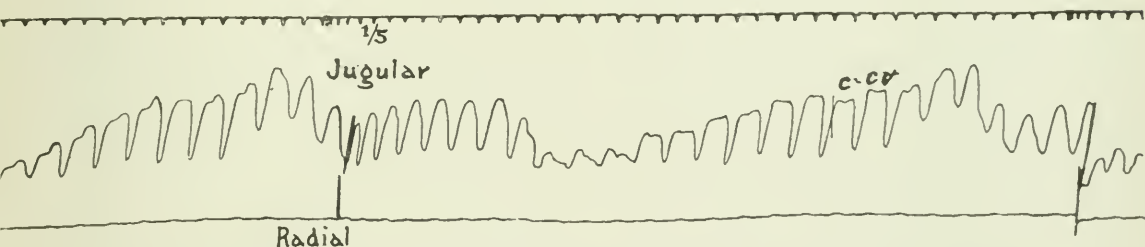


FIG. 2. A polygraphic curve taken during a paroxysm. Each radial cycle is accompanied by a plateau in the jugular curve, which plateau fills the systolic period. The rate is 61 per minute.

curves taken during the paroxysmal stage throw little light upon the actual mechanism present. The regularity of the radial tracing indicates the origin of the paroxysm from a single point in the heart musculature—a conclusion which is borne out by the electric findings.

Electro-cardiographic Curves.

The paroxysmal curves (Fig. 3, *IV*, *V*, and *VI*) were taken during the attack which occurred on April 23. The normal mechanism was present on the succeeding morning, and the corresponding curves (Fig. 3, *I*, *II*, and *III*) were then secured.

Curves *I* and *IV* represent leads from right arm to left arm, *II* and *V* are from right arm to left leg (these are standardized), *III* and *VI* are from left arm and left leg. The marks on the right-hand margin of curves *II* and *V* represent the deflexion obtained by throwing in $1/1,000$ volt, with the patient in circuit and the string at the sensitivity employed for the observations.

As is so usual in cases of paroxysmal tachycardia, the ventricular complexes of the curves from paroxysmal and slow periods show a close resemblance. The similarity in the right arm to left leg leads (*I* and *IV*) is most striking, though *S* is increased during the paroxysm. In the right arm to left arm lead of the paroxysm (*V*) *T* is partially inverted and *R* shows an absolute increase. In *II* the calculated value of *R* is 0.0019 volt; in *V* its calculated value is 0.0025 volt. This increase in *R* during the paroxysmal stage has been previously recorded, and it seems to be comparable to the occasional increase of *R* in the ventricular complex of premature auricular contractions. The latter is also frequently associated with partial inversion of *T*, as in this case. In the left arm to left leg lead *T* is partially inverted during the paroxysm (*VI*), while it is upright during the slow heart action (*III*).

The comparison of the outlines of the ventricular complexes, when fast and slow heart actions are present, clearly establishes the supraventricular origin of the paroxysm itself. They are complexes corresponding to beats which are started by impulses descending along the normal channels. The paroxysms have their origin, therefore, in auricle, auriculo-ventricular node or main bundle.

When attention is turned to the auricular representatives, the increased value of *P*, its broad and bifurcated summit, are indications of the auricular hypertrophy, and are compatible with the remaining clinical signs of mitral stenosis. The exaggeration of *R* in the left arm to left leg leads, and the diminution of *R* and exaggeration of *S* in the right arm to left arm leads, are indications of right ventricular hypertrophy and are equally consistent with the diagnosis of mitral stenosis.

The auricular complexes are conspicuous during the slow heart action. They are not to be found during the paroxysmal stage, and this fact is attributed, as it has been in previous cases, to the ectopic origin of the corresponding rhythm. The auricular complex is supposed to be isoelectric or nearly isoelectric, and its position consequently cannot be fixed in these curves. The *P-R* interval of the slow periods is 0.19 sec. The *P-R* interval of the paroxysmal stage is necessarily unknown.

The electric curves show no trace of those oscillations which are known to consort with fibrillation of the auricle, a condition which may therefore be excluded. The constancy in the type of complex from cycle to cycle, and the regularity of the sequence, demonstrate the origin of the paroxysm from a single focus in the heart muscle.

Summary.

1. A case of paroxysmal tachycardia is described, in which during the attacks the ventricular form of venous pulse was present. The paroxysms were of supraventricular origin, and probably arose as an ectopic rhythm from some portion of the auricular musculature.

2. The summit R , during the paroxysm, showed an increase of 0.0006 volt over the summit R of the slow periods, in the right arm to left leg lead. This increase of R is a common feature of paroxysmal tachycardia, as is also an accompanying decrease or inversion of T .

DESCRIPTION OF FIGURE.

FIG. 3. ($\times \frac{3}{5}$.) A series of electro-cardiographic curves, of which I , II and III were taken while the heart rate was within the normal limits, and of which IV , V and VI were taken during a paroxysm. I and IV were taken by means of a lead from the right arm to the left arm; II and V by means of a lead from right arm to left leg; and III and VI by means of a lead from left arm to left leg.

These curves show:—(1) The large P summit of the slow period, which is so characteristic of auricular hypertrophy; (2) a decrease of R in I , an increase of R in III , which is a common feature of right-sided ventricular hypertrophy; (3) the similarity of the ventricular complexes during the slow and fast mechanisms, proving the supraventricular origin of the paroxysms; (4) the absence of a defined P summit during the paroxysm, suggesting that the latter arises ectopically; (5) an absolute increase of R during the paroxysm (compare II and V in which $\frac{1}{1000}$ volt gives a similar deflexion); (6) partial or complete inversion of T during the paroxysms in the second and third leads.

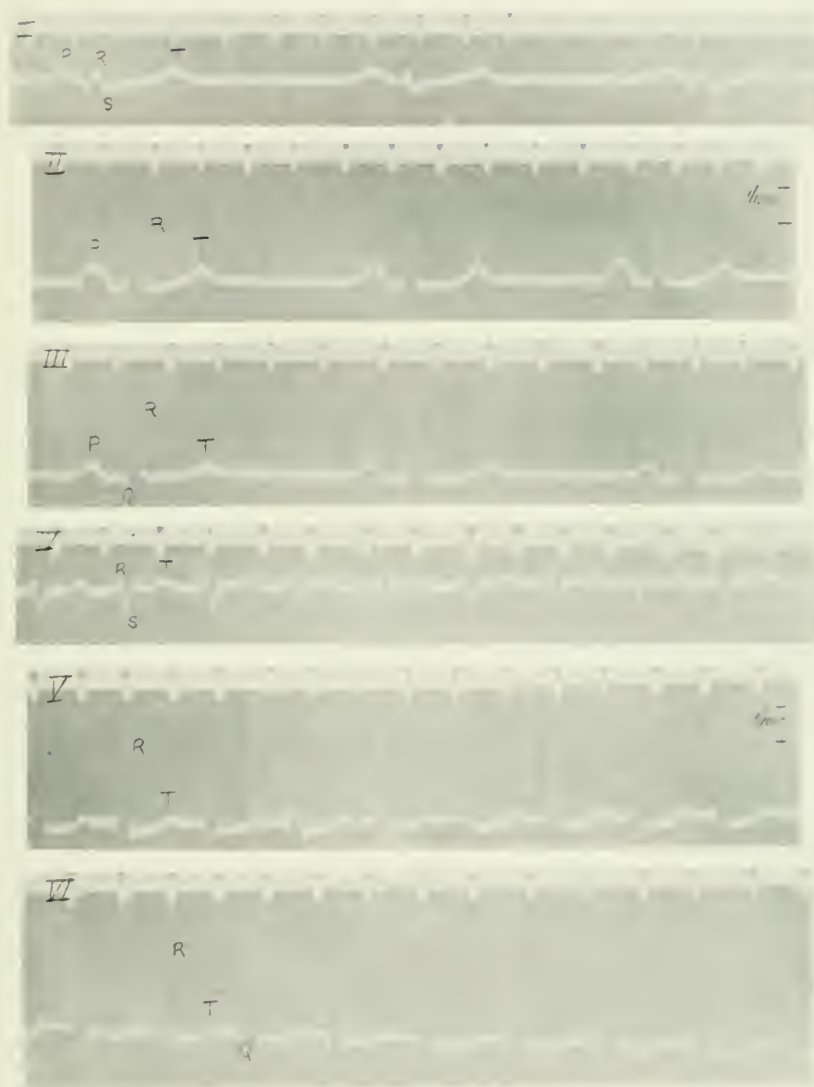


FIG. 3

THE ORIGIN OF THE ELECTRIC OSCILLATIONS AND THE DIRECTION OF CONTRACTION OF THE VENTRICLE IN INSTANCES OF COMPLETE IRREGULARITY OF THE HEART (AURICULAR FIBRILLATION)

By THOMAS LEWIS¹

(From University College Hospital Medical School)

With Plates 3 and 4

IN the present communication it is my desire to bring forward further evidence of two propositions. First, that the oscillations, which are so prominent in the electric curves of patients who exhibit complete irregularity of the heart, are produced in the auricular portion of the heart. And second, that the contraction wave takes the same course in the ventricle when complete irregularity is present and when the heart's mechanism is undisturbed, the ventricle responding regularly to auricle. A good deal of evidence has already (*Heart*, 1909-10, i. 306) been brought forward in support of each of these propositions. Thus, it has been shown that the oscillations referred to are independent of somatic muscle contraction and that, when the galvanometer which records them is connected to the patient by means of direct chest contacts, a lead from the vicinity of the right or superficial auricle yields maximal oscillations. It is also needful to demonstrate that, when direct chest leads are utilized, the occurrence of maximal oscillations in a lead from the vicinity of the right auricle is confined to cases of complete irregularity, and that this same lead also gives a large excursion at each contraction of a co-ordinately beating auricle.

Again, it has been demonstrated that in cases of complete irregularity the ventricular electric complex is of a type which is recognized as compatible with a contraction of the ventricle in response to auricle, that is to say with a contraction of the ventricle arising in a *supraventricular* impulse. For, when complete irregularity is present, each ventricular systole is accompanied by an *R* summit, and frequently by a summit *T*. The complete evidence required to substantiate the view that the direction of ventricular contraction is the same when the heart mechanism is normal and when the ventricle is irregular, is only to be obtained by securing the pictures given by a series of separate leads, and by a comparison of these pictures when one or other mechanism is present *and in the same subject*.

¹ Working under the tenure of a Beit Memorial Research Fellowship.

Observations.

The three leads originally devised by Einthoven, and now very generally adopted for clinical work, are shown in Fig. 1. The galvanometer is connected respectively to—

- I. Right arm and left arm.
- II. Right arm and left leg.
- III. Left arm and left leg.²

In each instance the first contact named represents that portion of the body which is connected to the lower end of the galvanometer string. For the purposes of the present observations I have utilized certain additional leads. They are :—

- IV. Sternum at second cartilage and inner end of fourth right interspace.
- V. Sternum at third cartilage and inner end of fifth right interspace.
- VI. Outer end of third left interspace and apex beat.
- VII. Epigastrium and apex beat.
- VIII. Sternum at second cartilage and apex beat.²

Copper disks $1\frac{3}{4}$ inches in diameter are used as contacts, and they are fastened to the chest by a stiff paste composed of flour, salt, and water.

The patient who was the subject of the observation suffered from shortness of breath on slight exertion and occasional swelling of the legs as a result of dropsy. The measurements of cardiac dullness in the supine posture were as follows :—Upper limit, third interspace ; right limit, $1\frac{1}{4}$ inches to right of mid-sternal line ; left limit, fifth space, $5\frac{1}{2}$ inches from the mid-sternal line. A systolic murmur was present at the apex, but no other physical signs were found in the heart.

The two series of observations recorded at the present time were made on the 4th and 17th of May, 1911. On the 4th the heart's mechanism was normal. On the 17th complete irregularity of twenty hours' duration was present. The area of heart dullness appeared to be the same on the two occasions. Both on the 4th and on the 17th a complete series of curves was obtained from the separate leads ; those of the 4th are shown in Fig. 2 ; those of the 17th are shown in Fig. 3. The two series of curves are placed side by side, the corresponding strips lying opposite to each other, so that comparison is facilitated, and the strips are numbered to correspond with the diagram of leads (Fig. 1).

In all the curves of Fig. 2 the beats are regularly spaced. In all those of Fig. 3 the irregularity is complete. The representative of auricular contraction (*P*) is present in greater or lesser degree in each strip of Fig. 2 ; it is absent in all the strips of Fig. 3, and is replaced by irregular oscillations of greater or lesser amplitude in each.

Considering the direct chest leads of Fig. 2 (*IV–VIII*),³ *P* is most prominent

² Baths of salt solution in which the limbs are immersed are used as contacts.

³ It is to be observed that, although amplitude is compared, the curves referred to are not fully standardized. The comparison is between one chest lead and another in a given series,

in strip *V*, the lead from sternum at third cartilage to inner end of fourth right interspace, and this is the lead which is in closest proximity to the right auricle. It is also well seen, though it is less marked, in leads *IV* and *VIII*; it is just perceptible in leads *VI* and *VII*.

Considering the direct chest leads of Fig. 3 (*IV-VIII*) the oscillations (*f*) are maximal in lead *V*, are clearly visible in leads *IV* and *VIII*, and are just visible in leads *VI* and *VII*.

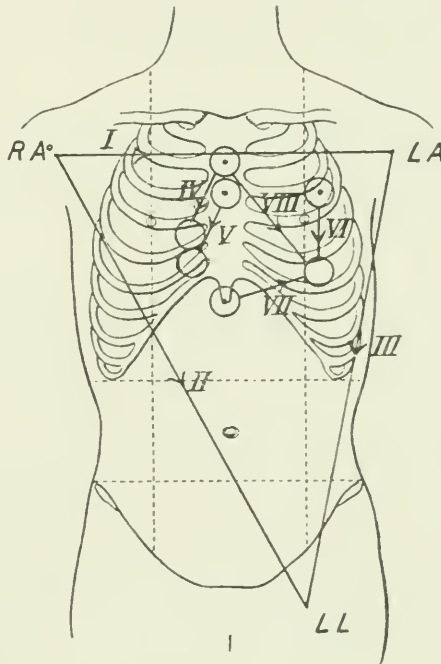


FIG. 1. A diagram showing the leads adopted in the recorded observations. *I*, *II* and *III* are the three leads adopted by Einthoven; *RA* = right arm; *LA* = left arm; *LL* = left leg. Leads *IV-VIII* are taken from fixed points on the chest wall, and are utilized in obtaining the purest pictures of auricular and ventricular electric effects.

The comparison between the two series of chest leads shows that the lead which gives the most prominent *P* summit, while the heart mechanism is normal, likewise yields the maximal oscillations when the heart is irregular. And the comparison may be extended to the whole series. The largest oscillations are shown in Fig. 3, *II* and *III*, the tallest *P* summits in Fig. 2, *II* and *III*; in Fig. 3, *I*, the oscillations are somewhat less prominent, in Fig. 2, *I*, *P* is less pronounced.

We consequently arrive at the conclusion that *when complete irregularity*

and the single possible variant is the resistance of tissue in one or other lead, for the same electrodes were employed from lead to lead and the string sensitivity remained constant throughout. Considering that the remaining resistance in circuit was approximately 10,000 ohms, any small variations in skin resistance from point to point are obviously negligible in so far as the main argument is concerned.

of the heart is present, the amplitude of the oscillations, in any given lead, is in proportion to the amplitude of 'P' in the same lead when the heart mechanism is normal. It is upon this conclusion that we may now base the assertion that the electric oscillations, recorded when the heart is completely irregular, are of auricular origin.

We may now turn to the second proposition, i. e. that which deals with the direction in which the ventricular contraction is propagated. The object of clearly demonstrating that the direction of contraction is the same, while normal mechanism is present and while the heart beats in a completely irregular fashion, will be evident. Under the former circumstance the ventricle receives its impulses from the co-ordinately beating auricle, and it is desirable to show that it receives its impulses from the auricular tissue under the last-mentioned condition. The proof of similar direction of contraction rests upon a careful comparison of the ventricular portions of the curves shown in the corresponding strips. In Fig. 2, *I*, the ventricular complex consists of *Q*, *R* and *T* summits. These are also present and have a similar outline in Fig. 3, *I*. In Figs. 2, *II*, and 3, *II*, *Q*, *R*, *S* and *T* summits are seen and again the outlines are similar. In Fig. 2, *III*, *R* is small, *S* is deep and has a slight notch on the downstroke; the same features are found in Fig. 3, *III*. A comparison of the direct chest leads (*IV-VIII*) is equally convincing; summit for summit the curves correspond, and they differ solely in minor changes of amplitude, and in the fact that in the curves of Fig. 3 the inconspicuous and broad summits of the later phases of systole are distorted in some measure by the oscillations.

We may conclude, therefore, that *the electric changes of the ventricle shown by a series of leads from fixed points are qualitatively identical, whether such leads are taken when the heart mechanism is normal, or whether they are taken at a time when the ventricle is completely irregular.* And this conclusion confirms the previously adopted view that when the heart is affected by this specific disorder of its mechanism the impulses reach the ventricle from a supraventricular source.

The two main contentions, the origin of the oscillations in the auricle and the passage of the impulses which originate ventricular contractions along the normal channels, in patients who are the subject of ventricular irregularity, are in every way compatible with a previously expressed conclusion that in such patients the auricle is in a state of fibrillation.



FIG. 2

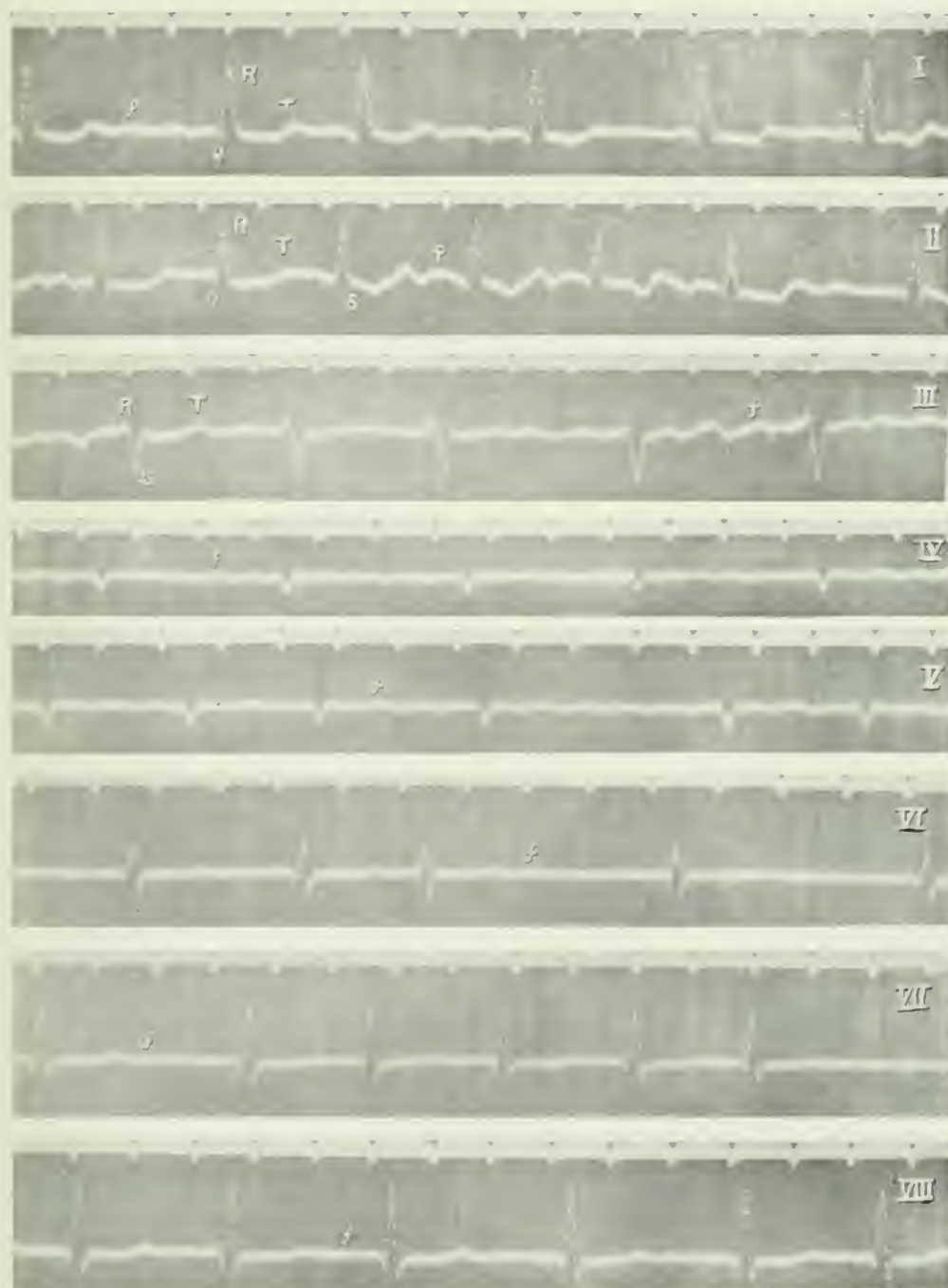


FIG. 3

THE RESPONSE OF NORMAL AND ABNORMAL MUSCLE TO LEDUC'S INTERRUPTED CURRENT.

BY OTTO MAY, M.D. (BEIT RESEARCH FELLOW).

(From the Research Department, University College Hospital Medical School.)

AT the Congress of the French Association for the Advancement of Science, held at Angers in 1903, Professor S. Leduc, of Nantes, described a form of electrical current, the aim of which was to produce a given excitation with a minimum expenditure of energy. It consists of a galvanic current, rapidly interrupted, and with the "make" forming a definite known proportion of each period. For its production he devised a special interrupter (driven by an electric motor), which is fully described and figured in the *Archives d'Electricité Médicale* (Bordeaux), November 25, 1908. It enables the current to be interrupted at rates of 20 to 200 per second, the frequency being recorded by a special counter attached. Further, in each resulting period the time of "make" can be varied from $\frac{1}{100}$ to $\frac{7}{100}$ of the total period. The current thus obtained may be represented graphically by the annexed diagram (fig. 1).

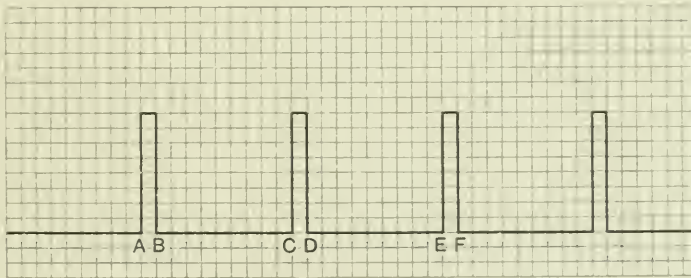


FIG. 1.—Scheme of current obtained with Leduc's Interrupter. In this figure, each period of "make," AB, CD, EF, is $\frac{1}{10}$ of the total period. AC, CE, &c.

The duration of each complete period (make and break), AC, CE, &c., varies from $\frac{1}{20}$ (.05) second to $\frac{1}{200}$ (.005) second. In each such

period, the ratio AB/AC, CD/CE, &c., can be regulated between the limits $\frac{1}{100}$ and $\frac{70}{100}$. It follows, therefore, that the actual duration of each contact can be varied from $\frac{1}{100}$ of $\cdot 005 = \cdot 00005$ second to $\frac{70}{100}$ of $\cdot 05 = \cdot 035$ second.

By the use of this current, the phenomena usually associated with the faradization of muscle can be reproduced, with this added advantage, that all the factors of the stimulating current are susceptible of direct measurement and delicate gradation. Thus the strength, duration and frequency of the stimulus are all under control, and can be varied independently of one another. As suggested by Leduc (op. cit.), this type of current should be eminently serviceable for the clinical examination of human muscle. It was for the purpose of obtaining the requisite data for such clinical employment that the experiments described below were performed.

I.—THE RESPONSE OF NORMAL MUSCLE.

As these experiments were made with a view to applying the results to man, it was, of course, essential to use mammalian muscle for the purpose. In every case cats were employed, and were kept fully anæsthetized throughout the experiment. Two sets of muscles were investigated: (*a*) a flexor group—the soleus-gastrocnemius; (*b*) an extensor group—the quadriceps of the thigh. The results were practically identical in the two cases; the former was, however, a more convenient preparation to work with, so most of the experiments were done with it. Except where otherwise stated, the results here detailed were obtained from the gastrocnemius.

The preparation was made as follows: The skin of the calf was reflected, care being taken to avoid hæmorrhage from the large superficial veins. The calf-muscles were then freed from the musculo-tendinous expansions of the hamstrings which run down on either side towards the tendo Achillis. The latter was then separated from its bony attachment, and the superficial muscles (soleus and gastrocnemius) carefully dissected from the deep flexors, nearly up to their origin. The tendo Achillis was then connected by a suitable thread to a "Keith Lucas Rectilinear Myograph" (weighted with 50 to 120 grm.), arranged to write on the smoked paper of a kymograph. Two platinum-iridium wire electrodes were then passed through the upper and lower parts of the muscle, and connected to the kathode and anode of the stimulating circuit. During the whole experiment the muscle

preparation was kept warm and moist by irrigation with "normal saline" at body temperature.

The source of the current was the main supply (220 volts continuous, passed through a lamp resistance, and a suitable rheostat for grading the voltage). This was in series with a milliamperemeter and a Leduc Interrupter (made by Gaiffe, of Paris), with special counter attached. The circuit, which also contained a "Post-Office" make-and-break key, was completed by the wire electrodes.

As regards the measurement of the current, the amperemeter gave a steady reading with all rates of interruption from twenty per second upwards. If each "make" was $\frac{x}{100}$ of the total period, then the reading would be $\frac{x}{100}$ of the actual current. Thus, with the scale at 10 ("make" = $\frac{10}{100}$ of each period), a reading of .2 milliamperes corresponds to an actual current of 2 milliamperes (uninterrupted).

The tracings were taken on a stationary drum which was moved by hand between each observation. The contractions were obtained by momentarily pressing the make-and-break key. In addition, a series of contractions were recorded on a moving drum, with the usual signal to register the period of stimulation.

Results.

(In all the succeeding matter, the fractions $\frac{1}{100}$, $\frac{2}{100}$, $\frac{x}{100}$ may be taken as referring to the ratio make: total period, as previously indicated.)

Fig. 2 represents the typical response of normal muscle to the Leduc current, with constant ratio of make: total period (in this case $\frac{10}{100}$), but with varying frequency of interruption. It will be seen that, as the frequency of interruption is increased from 20 to 120 per second, the heights of contraction increase; from 120 to 200, the heights are approximately equal, though there is a slight tendency to diminution. A large number of experiments of this type was made; in every case the increase with increasing speed was obtained, though the *optimum frequency* was not quite constant. It varied between the limits of 90 and 120. Thus in fig. 3 the maximum contraction is obtained at 100. This tracing shows another point of interest, namely, the more marked decrease obtained as the frequency was increased from 100 to 200. This was noted in several cases, though the majority of tracings obtained were of the type shown in fig. 2. It may be noted then, that all agree in the initial rise to a maximum between the limits 90 and

120, but that there is a divergence as regards the shape of the remainder of the tracing. In some, the gradient of decline is considerably more marked than in others. The significance of this difference will be discussed later.

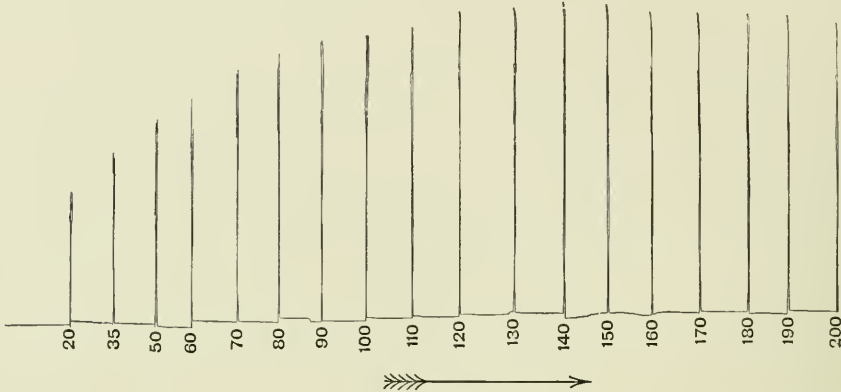


FIG. 2.—Normal gastrocnemius; tracing of contraction, with constant ratio $\frac{10}{100}$, and gradually increasing frequency of interruption (figures below curves of contraction represent the number of interruptions per second). From L. to R.

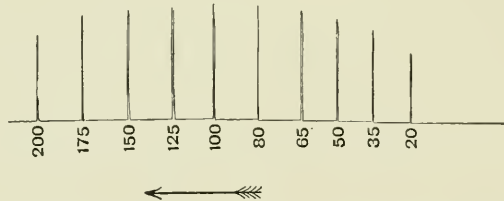


FIG. 3.—Normal gastrocnemius (cf. fig. 2). This tracing shows the tendency seen in some cases for the contractions to diminish with increasing frequency. From R. to L. (See text.)

If the frequency, instead of being increased from 20 to 200, is diminished, step by step, from 200 to 20, the tracing obtained is the negative image of those just described—i.e., the relation of height to frequency is the same. Further, it is independent of the ratio make : total period, as long as this does not fall below $\frac{5}{100}$ (*v.i.*). Nor is it affected by changes in the strength of the current; provided this is submaximal, the curve shows the same features with varying strength of current.

Fig. 4 shows the result of stimulation of the trunk of the sciatic nerve with a very weak current, $\frac{5}{100}$, at varying frequency. In this, the relation of height of contraction to frequency of interruption is not unlike fig. 2; it differs, however, in having its optimum frequency at about 170, instead of 120.

In a current employed in the manner indicated, in which the ratio $\frac{x}{100}$ remains constant, while the frequency of the interruption varies, there are really two variable factors to consider: (a) the absolute duration of each "make" period; (b) the frequency of interruption.

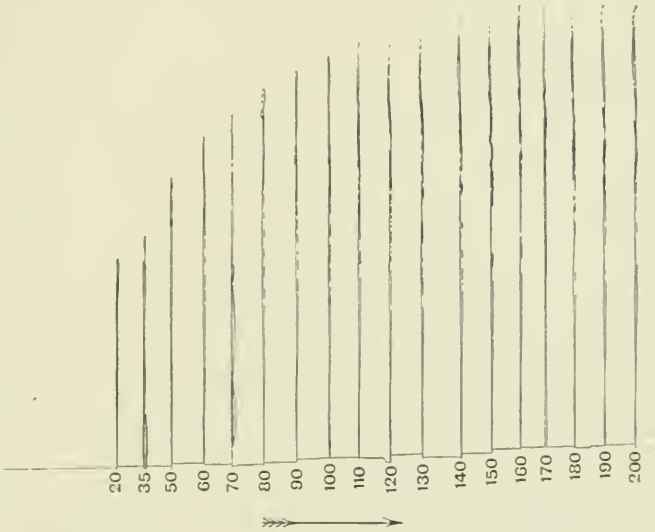


FIG. 4.—Normal gastrocnemius: contractions obtained by stimulating the sciatic nerve with very weak current; contact ratio $\frac{5}{100}$; gradually increasing frequency.

Thus, when the make is $\frac{10}{100}$ of each period, its actual duration at a frequency of 20 per second is $\frac{1}{200} = .005$ second, while, with a frequency of 100 per second, this is reduced to $\frac{1}{1000} = .001$ second. Hence it follows that, in the experiments just described, the duration of each "make" diminishes proportionately with the increase of frequency. Consequently a series of observations was made with a view to estimating separately the influence of these two variables.

(a) *Keeping the Frequency constant, but varying the actual duration of "Make."*

If the interruptions are kept constant, say at 100 per second, and the ratio $\frac{x}{100}$ is gradually increased from $\frac{1}{100}$ to $\frac{60}{100}$, it is found that

the height of the contractions increases till x reaches 5—i.e., until the duration of each “make” is $\frac{5}{100}$ of $\frac{1}{100} = \cdot 0005$ second—thence onwards the contractions remain approximately equal. The same result is obtained if the value of x is gradually diminished from 20 to 1 (fig. 5). The corresponding values of x at other rates of interruption are given approximately in the following table:—

Rate of interruption per second			Minimum value of “ x ” for optimum contraction (mean of several observations)			Actual period of “make”
50	3	·0006 sec.
75	4·5	·0006 „
100	5	·0005 „
125	6	·00048 „
150	7	·00046 „

It seems, therefore, that for each rate of interruption there is a *limiting value* of “make” period beyond which the efficiency of the current is not increased by increase of its duration.

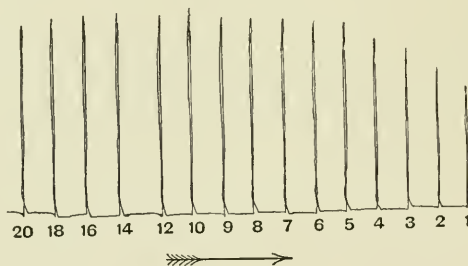


FIG. 5.—Normal gastrocnemius; tracings obtained with constant frequency of 100; ratio $\frac{x}{100}$ gradually diminished from $\frac{20}{100}$ to $\frac{1}{100}$. L. to R.

It is a matter of interest to consider this result from the point of view of Nernst's theories of the stimulating effect of the constant current. He assumes that the exciting effect of such a current can be due to ionic displacement only, and suggests that it is proportional to the changes in concentration of ions at the surface of semi-permeable membranes [6]. He has calculated that the change (c) produced by a constant current (i) of short duration (t) is proportional to $i \sqrt{t}$. In other words, the concentration changes, and therefore the stimulation efficiency, varies as the product of the strength of the current and the square root of the time (see also Keith Lucas [3] and Hill [1]). This formula holds only for very small values of “ t ”; a limit is soon reached at which “accommodation” occurs, due to a reverse passage of ions

which tends completely to neutralize that due to the current.¹ The upper limit of time for which this formula holds good in the case of the frog's sartorius was found to be '01 second (Keith Lucas) [4].

Now in fig. 5 it is seen that the height of contraction from $\frac{20}{100}$ to $\frac{50}{100}$ are equal. The frequency of interruption was constant (100); hence it is justifiable to assume that the exciting value of each "make" was equal, though their periods varied. In other words, for normal cat's gastrocnemius, with complete innervation, the *limiting time*, above which "accommodation" (in Nernst's sense) comes into full play, is of the order of '0005 second, and therefore very much below the figure obtained by Lucas for the frog's sartorius (see further, below).

It will be noticed that the figures given in the above table show a slight diminution as the frequency increases, being '0006 second for 50, and '00046 for 150. I can give no explanation of this discrepancy, but the figures are sufficiently concordant to serve the purpose for which they are intended to be used (*see p. 288*).

(b) *Keeping the Period of "Make" constant, but varying the Frequency of Interruption.*

A series of observations was made in which the value of "x" was made to vary directly as the frequency of interruption, as follows:—

Frequency		Value of "x"		Actual period of "make"
20	..	1	..	'0005 sec.
40	..	2	..	"
60	..	3	..	"
80	..	4	..	"
100	..	5	..	"
120	..	6	..	"
140	..	7	..	"
160	..	8	..	"
180	..	9	..	"
200	..	10	..	"

Similar observations were made in which the "make" period was kept constant at '001 and '002 second respectively. The results obtained were practically identical in the three cases. Fig. 6 shows the record of such an experiment. It will be seen that the result is very similar to fig. 2—i.e., the size of the contractions increases with increasing frequency up to 120, and then remains approximately constant. This is what one would expect, bearing in mind the results obtained with constant frequency (*v.s.*). For, with a value of $\frac{x}{100} = \frac{10}{100}$, the actual period of each "make" never falls below

¹ This "accommodation" may be compared to that postulated by Hering in his theory of metabolism, in which dissimilation leads automatically to assimilation, and *vice versa*.

the value '0005 second, determined as the "accommodation" limit for this muscle. This factor, the period of each make, does not therefore play any part in determining the size of the contractions; the only other variable is the frequency of interruption, and, as we see, this is in itself sufficient to produce the result shown in fig. 2.

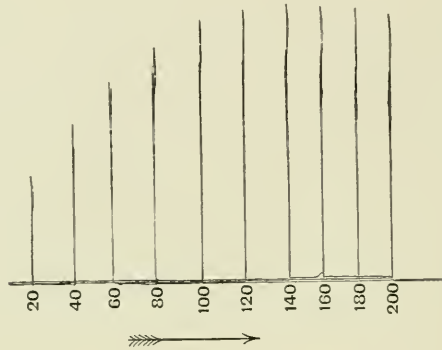


FIG. 6.—Normal gastrocnemius; tracings obtained with constant period of make ('005 sec.), but with varying frequency of interruption (20 to 200).

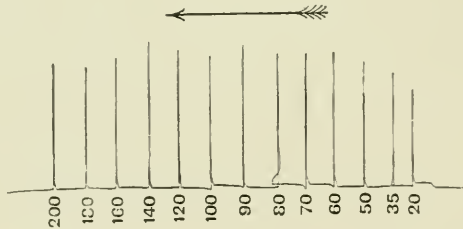


FIG. 7.—Normal gastrocnemius; constant ratio $\frac{1}{100}$; varying frequency from 20 to 200 interruptions per second. R. to L. (See text.)

The conditions are, however, different if, instead of $\frac{1}{100}$, we employ a smaller value—e.g., $\frac{1}{1000}$ —and vary the frequency. In this case, as soon as the frequency is increased beyond 20 per second, the actual period of make falls below the limiting value, and becomes progressively more so as the speed is increased. In this case, therefore, there are two variable factors at work, of opposite sign—(a) the increasing frequency, tending to increase the size of the contractions, and (b) the diminishing periods of make, tending to diminish the contractions. Fig. 7 shows the tracing from such an experiment. It will be seen

to differ from fig. 2, in that it fails to show the regular increase to a maximum of 100 to 120, but has an irregularity dependent on the conflicting gradients of these two opposing factors.

II.—THE RESPONSE OF CURARIZED MUSCLE.

To investigate the response of muscle in which the motor end-plates had been paralyzed by curare, a series of observations was made on cats after intravenous injection of a 2 per cent. solution of curare, artificial respiration being maintained by a Brodie's pump (with chloroform in the air-chamber). The efficiency of the injection was always tested by stimulation of the nerve-trunk.

The strength of current necessary to produce a fair-sized contraction was much greater than for normal muscle; the weaker currents produced only a local contraction in the neighbourhood of the electrodes. Further, the shape of curve obtained with constant ratio—e.g., $\frac{1}{100}$ —and gradually increasing frequencies showed a considerable difference from those above considered. Instead of a maximum at 90 to 120, the curarized muscle showed one at 50 to 70, followed by a sharp decline, so that with a ratio $\frac{1}{100}$, and current-strength '6 ma. (r.s.), no contraction at all was obtained with a frequency of 200¹ (cf. fig. 8).

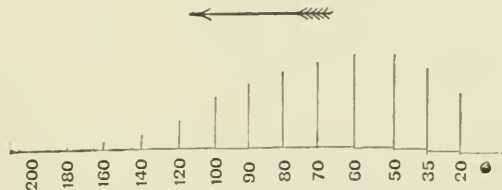


FIG. 8.—Curarized gastrocnemius; tracing of effect of strong current. Ratio $\frac{1}{100}$; varying frequency of interruption 20 to 200 per second. R. to L.

Comparing the curves for curarized muscle, normal muscle, and nerve-trunk, it will be seen that the response of normal muscle is, in a sense, intermediate between the other two—nerve-trunk and curarized muscle. Thus, the optimum frequency for nerve is 170 and onwards (cf. fig. 4), for curarized muscle 50 to 70, and for normal muscle 100 to 120. This suggests that when a muscle is subjected to direct

¹ If, however, the strength of current is sufficiently increased, curarized, like normal muscle, will show definite contraction even with ratio $\frac{1}{100}$, and speed of 200—i.e., with stimuli of only '00005 second duration.

stimulation in the manner described, the contraction is a composite one, resulting partly from stimulation of the intramuscular nerve-trunks, and partly from direct stimulation of the muscle-fibres themselves.

We are now in a position to discuss the significance of the variation noted on p. 274, as regards the optimum frequency of interruption and the gradient of decline (if any) in normal muscle. At first I was inclined to regard the curves of the type shown in fig. 3 as due to damage to the muscle from hæmorrhage, excessive exposure, &c. But the observations detailed in the following section make it improbable that these factors play any great rôle in the genesis of these variations. A more likely explanation is the relative predominance in any particular case of the two factors—nervous and muscular. If a relatively large intramuscular nerve-trunk happens to be near the electrode, then the response approximates more to the “nervous” type, while, if fewer nerve-fibres are stimulated, the response will show an optimum at a rather lower frequency, and a more marked gradient of fall as the frequency approaches the 200 limit.

Curarized muscle shows another difference from normal muscle, of particular interest in view of the results obtained after nerve-section (*v.* Section IV). The “limiting period,” instead of being about $\cdot0005$ second, has a value about six times as great, about $\cdot0033$ second. This is shown by the following figures (*cf.* p. 277):—

Rate of interruption per second	Minimum value of “x” for optimum contraction		Actual period of “make,”	
50	..	18	..	$\cdot0036$ sec.
100	..	30	..	$\cdot0030$ „
150	..	50	..	$\cdot0033$ „

It cannot, of course, be assumed that these results represent those that would be obtained from perfectly normal muscle deprived of its nerve, as one must bear in mind the possibility of a toxic effect of curare on the muscle-tissue itself. Such an effect does not, however, seem to be at all prominent, as was shown by the following experiment: 1·5 c.c. of the curare solution was injected intravenously, and produced complete paralysis of the motor nerve-endings. The response to direct stimulation was as above indicated; 3 c.c. more curare was then injected gradually, and more applied directly to the muscle, but the response was not further affected; it still gave an optimum at a frequency of 60, with about the same gradient of decline with increasing frequency.

III.—RESPONSE OF EXHAUSTED AND DYING MUSCLE.

After a muscle has been stimulated with strong tetanizing currents for long periods (five to fifteen minutes) the response obtained is somewhat similar to that just described for curarized muscle—i.e., an optimum at a frequency of 60 to 80, and a steeper gradient of decline from this point with increasing frequency. It seems, indeed, that the prolonged stimulation actually causes temporary paralysis of the motor end-plates, as is shown by the fact that if the stimulus is applied to the nerve-trunk the response gradually disappears, to return if the stimulus is then thrown direct into the muscle (by a Pohl's commutator without cross-wires). As a rule, however, the effect produced by this method is not quite so marked as with curare; the optimum never fell to 50, as it did in the case of the latter drug.

This modified response of exhausted muscle is of comparatively brief duration; after two to three minutes the normal response reappears—i.e., the motor end-plates recover their conductivity in this time.

The gradual alterations of excitability in the muscle following the death of the animal were examined in several cases. Immediately after death (by bleeding or pithing), the response shows no deviation from the normal; five minutes later the optimum was still 100, and the gradient of decline with increasing frequency very gradual. The following table shows the approximate findings at varying periods after death:—

Minutes after death	$\frac{x}{100} = \frac{10}{100}$				Gradient of decline
	Optimum				
5	..	100	..		Slight
15	..	80—90	..		Slight
20	..	60—70	..		Rather steeper
25	..	50—60	..		" "
45	..	50	..		Steeper
60	..	20—25	..		Steep
90	..	20	..		Very steep (no contraction at greater frequency than 100 with quite strong currents)

In other words, after about an hour the muscle of a dead cat behaves in a manner very similar to the "degenerated" muscle resulting from nerve-section.

IV.—THE RESPONSE OF DEGENERATED MUSCLE.

To examine the response of muscle at varying periods after nerve-section, the left sciatic was resected in the middle of the thigh in a

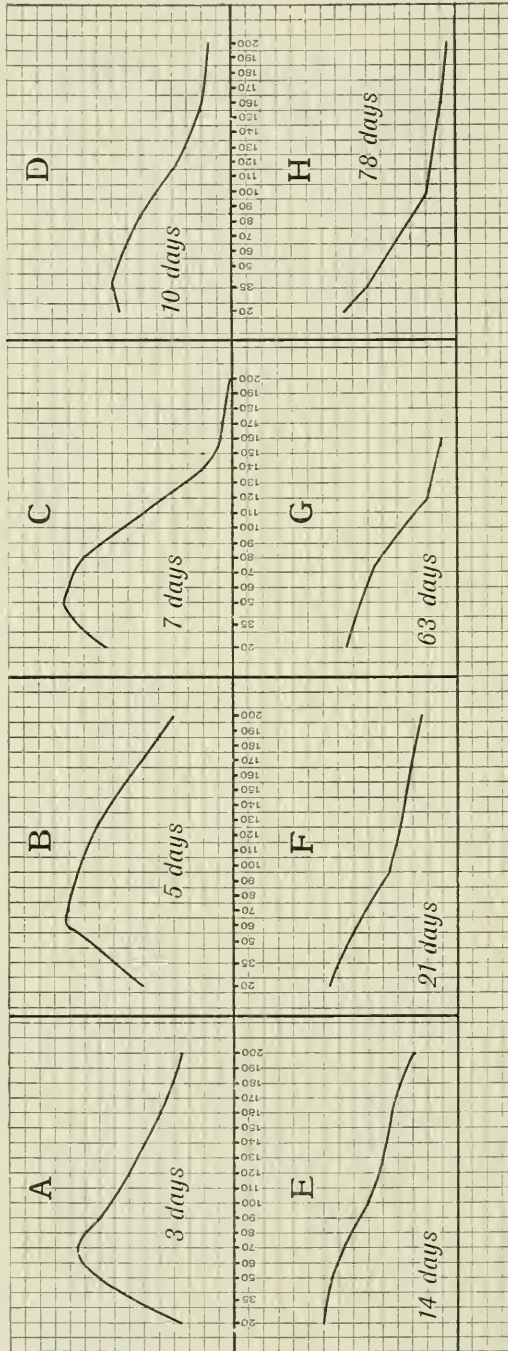


FIG. 9.—Diagram of curves plotted to show relation of height of contraction to frequency of interruption in a series of gastrocnemii at various intervals after sciatic nerve section. In all, constant ratio $1\frac{1}{2}$; frequency of interruption varied from 20 to 200 per second.

series of cats, with strict antiseptic precautions. At a suitable period after operation the gastrocnemius was tested in the usual way.

The results are exhibited graphically in fig. 9, which shows the response to gradually increasing frequencies of interruption, at periods varying from three to seventy-eight days. From this it will be seen that, as the time after nerve section increases, the *optimum frequency* diminishes, until, from fourteen days onwards, the curve falls gradually from the beginning. In other words, when a certain stage of "degeneration" is reached, the best contraction for any given value of $\frac{x}{100}$ —e.g., $\frac{10}{100}$ —is with a frequency of 20; as this is increased, the contractions become steadily less. The following table gives the optimum for various times:—

Days		Optimum frequency
3	..	70
5	..	60
7	..	50
10	..	35—50
14	..	20—35
21	..	20
63	..	20
78	..	20

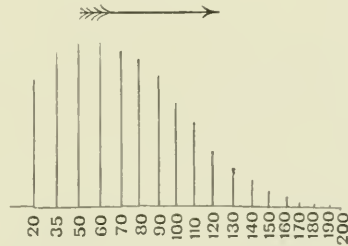


FIG. 10.—Gastrocnemius seven days after sciatic section; tracing of contractions; constant ratio $\frac{10}{100}$; varying frequency of interruption 20 to 200 per second. L. to R.

Fig. 10 is the actual tracing from a gastrocnemius seven days after section of its nerve. A comparison with fig. 2, from a normal cat, shows a striking difference, not only as regards the shifting backwards of the optimum, but still more in the gradient of descent from this point onwards.

The functional change in denervated muscle is brought out equally well by an examination of the results of varying the ratio $\frac{x}{100}$, with constant speed of interruption. Unfortunately this was not completely investigated in all the cases, but the following figures suffice to

show how the “*limiting time*” (in the sense explained on p. 278) is increased in these conditions. In the following table, the frequency of interruptions is 100 in each case.

Days after nerve-section		Minimum optimum value of $\frac{x}{100}$		“Limiting time”
5	..	$\frac{1.8}{100}$..	·0018 sec.
7	..	$\frac{3.0}{100}$..	·003 ”
10	..	$\frac{4.0}{100}$..	·004 ”
14	..	$\frac{4.0}{100}$..	·004 ”
21	..	$\frac{4.0}{100}$..	·004 ”

It is interesting to note that, seven days after section (fig. 11) the value, ·003 second, is approximately the same as for curarized muscle. This is in harmony with the fact that, at this stage, the peripheral part of the cut nerve is no longer excitable: after five days, on the other hand, this loss was not quite complete.

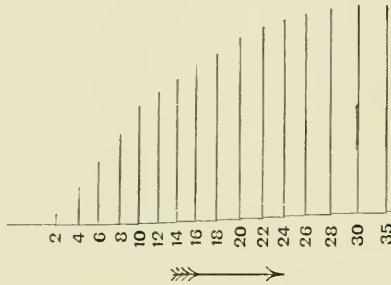


FIG. 11.—Gastrocnemius seven days after sciatic section; tracing of contractions with constant frequency of interruption (100 per second); ratio $\frac{x}{100}$, varied from $\frac{2}{100}$ to $\frac{35}{100}$. L. to R.

It seems that, from ten to twenty-one days, the value of this factor remains approximately constant. This method of examination had not been carried out in the other animals which had been allowed to survive longer—sixty-three and seventy-eight days respectively, so that information is lacking as to whether the “*limiting time*” is further increased in these cases. I had the opportunity, however, of making some observations on animals in which a motor nerve had been damaged in other ways.

Fig. 12 shows the tracing from the rectus femoris of a cat, sixty-one days after the injection of alcohol into the anterior crural nerve. It will be seen that it shows an optimum frequency of 20—a typical “*reaction of degeneration*.”

In another cat the gastrocnemius was examined thirty-nine days after the sciatic nerve had been seriously damaged by being crushed with Spencer-Wells forceps. In this animal the clinical symptoms were at first like those of a complete nerve-section, but recovery was more rapid than after actual cutting of the nerve. The optimum frequency was 70, and the "limiting time" '0012 second—i.e., the condition of the muscle was functionally similar to one three days after nerve-section. Histologically (by Bielschowsky's method), the distal part of the nerve was found to be in a fairly advanced state of regeneration, showing numerous rather fine axones, without a medullary sheath, but closely associated with many "apotrophic cells" (Marinesco).



FIG. 12.—Rectus femoris of cat sixty-one days after injection of alcohol into anterior crural nerve. Tracing of contractions, with constant ratio $\frac{R}{L}$, and varying frequency of interruption, 20 to 200. R. to L.

In a third cat, the sciatic had been tightly ligatured with silk one hundred and one days before examination. This injury retards regeneration to a greater extent than simple section, owing to the fibrosis produced by the unabsorbable silk. However, the muscles were on the road to recovery, as the optimum frequency was 50, and the "limiting time" '0016 second—i.e., the muscle had returned to a functional condition about equal to that shown five days after nerve-section.

From the results here detailed, it seems then that about seven days after nerve-section the muscle behaves very like one under the influence of curare. After two or three weeks it appears to get into a fairly stable condition, which persists until regeneration begins.¹

¹ Though the functional condition appears to become stationary, the actual weight of the muscle undergoes progressive diminution for a much longer period.

V.—THE CLINICAL APPLICATION OF THE RESULTS.

The question may well be asked, "Is there any need for new methods of examining the electrical reactions of muscles, or is the present system, that of Duchenne and Erb, entirely satisfactory?" I venture to think that all those actually engaged in this work, and who are therefore in a position to appreciate its difficulties, will agree that it falls far short of practical perfection. A brief review of the method will suffice to indicate some of its defects. In the first place, the faradic current, as ordinarily employed, is quite incapable of anything approaching accurate measurement as regards any of its factors—frequency of interruption, voltage of the induced current, &c. As regards the galvanic examination, the investigator aims at measuring the least current which will just produce a contraction of the given muscle at "make," (*a*) when the kathode, (*b*) when the anode, is the stimulating electrode used. He finds in practice, however, that this is by no means easy, even in the case of any given muscle. With constant voltage, the current-strength, as indicated by the milliamperemeter, tends to be anything but constant, owing to the continually varying resistance of the circuit (due partly to the electrolytic changes in the tissues, and partly to varying contact of the electrode with the skin). Further, he has no means of knowing how much of any given current actually reaches the muscle; apart from the size of the electrode, this will be influenced by the depth of the muscle, the amount of subcutaneous fat, the texture of the skin, &c. In many text-books stress is laid on this part of the examination, from the point of view of determining whether Pflüger's Law ($K.C.C. > A.C.C.$) holds, or whether there is the "polar reversal" said to be characteristic of degenerated muscle. As a matter of fact, it is by no means constantly observed, and Wiener and Page May state that there is no real reversal, but only an apparent one, due to relative spread of the peripolar zone under these conditions.¹ The really important point to be insisted upon in the galvanic examination is the *quality* of the response—whether the normal rapid twitch is obtained, or a more sluggish contraction. In the estimation of this there is ample scope for the "personal equation," or perhaps it would be truer to say that a very large experience is necessary in order adequately to judge its character. Lastly, there is the important practical point that the galvanic examination is a painful

¹ In a recent monograph, however, E. Reiss [7] claims to have produced it under rigorous experimental conditions in frog's muscle by the action of K and NH_4 ions in suitable concentrations.

one—an especial difficulty in the case of children. The chief drawbacks, then, to this method are—the large number of unmeasured and unmeasurable factors concerned in the contractions, the difficulty of estimating the quality of the galvanic response, and the painful character of the examination.

If one judges by the enormous literature of the subject, it would seem that many investigators have been seeking a more exact method of estimating the functional condition of human muscle. Thus Zanietowski [8] has been the pioneer of a mass of work dealing with the response of muscle to condenser discharge; he and others have shown that degenerated muscle needs a higher voltage and slower discharge than does normal. In spite, however, of the many advantages claimed for this method, it has never come into anything like general use, at any rate in this country.

Mendelssohn [5] has suggested that one of the so-called “Wedensky Effects” might be turned to clinical utility. If muscle is subjected to prolonged tetanization at a given frequency and with a given strength of current, it is found that the height of contraction gradually diminishes. By suitably diminishing the frequency, the contraction can then be restored to its original height. For any given condition of a muscle, there appears to be a corresponding “optimum frequency.” Mendelssohn accordingly suggests that this phenomenon might profitably be utilized for clinical purposes, but up to the present his suggestion does not appear to have been acted upon. -

It is obvious that this is a special application of a principle closely analogous to that underlying the investigations described in this paper. The essential advantage of a method such as the one outlined below is, that during an investigation all the conditions remain constant except one (frequency of interruption, or ratio of make to break), which is varied in an exact, quantitative manner. *The knowledge of the muscle's condition is obtained, not by comparing its contractions with those of other muscles, but by a consideration of the variations of the actual responses of the muscle itself to known changes in the stimulus.*

At this stage I think it well to point out once more that the object of these experiments was to find data for the clinical employment of Leduc's current for muscle-testing. No meticulous accuracy is claimed for the results; for example, no attempt was made to calibrate the speed-counter attached to the interrupter, nor were steps taken to control any possible variations in the voltage of the current from the main. These defects, while perhaps sufficient to compromise the results if

claims were made to absolute mathematical exactitude, do not, in my opinion, invalidate the findings in their clinical application.

In considering how the results here detailed could best be applied for this purpose, one is faced with the question as to the practicability of applying the graphic method to man. This has been the subject of many investigations, and a large number of workers have published results obtained by various methods.¹ The most recent, as far as I am aware, is that of Larat [2]. He employs an apparatus consisting of an armlet, inextensible except in a small part of its length, which here consists of a thin india-rubber membrane. At either extremity of the membrane is a circular metal upright, joined to its fellow by a rubber bellows. This is in turn connected to an air-tambour writing on a revolving drum. The armlet is adjusted to the limb, and the muscle suitably stimulated. Any increase in girth at the level of application of the armlet stretches the thin rubber, which in turn opens the bellows and produces a fall of the tambour lever. In his book, Larat gives a large number of tracings obtained by this method. The latter, however, like the earlier ones, including the ergograph, has many obvious disadvantages. The chief of these are: (a) The more or less elaborate apparatus required, and the difficulty of satisfactory adjustment, a serious drawback for clinical work; (b) their limited applicability: while they may be fairly satisfactory for limb-muscles, none is really applicable either to the face or trunk; (c) in none of them, except perhaps the ergograph (which is of use only for the fingers or hand), is there any exact quantitative relation between the strength of the contraction and the magnitude of the lever's excursion.

For all these reasons I think that none of the present graphic methods will ever take a permanent place in routine clinical work. I have spent a good deal of time in trying Larat's and other methods, and in endeavouring to solve the problem of combining satisfactorily an electrode and recording apparatus, so that the actual contraction at the point of stimulation can be conveniently registered, but so far without much success.

It seems to me, nevertheless, that the experimental results should be capable of clinical application without the necessity of any such graphic record, however desirable the latter may be as a refinement. The testing could best be carried out as follows:—

Begin with the ratio make : total period at 10 : 100, and frequency of interruption 100. Adjust the strength of current till a contraction

¹ For list of these, see Mendelssohn's article in *Beruttau's Handbuch* [5].

is just obtained. Now, keeping everything else constant, diminish the frequency to 20 or 25. Normal muscle should no longer give a contraction, but degenerated muscle will give a much better one. Alter the frequency gradually from 20 to 200, and decide as far as possible which is the optimum. Or, better, keep the frequency constant at 100, and vary the contact-ratio (x). For normal muscle, the size of the contractions should be independent of the value of x between the limits 5 and 50. For degenerated muscle, the size of the contractions should increase as x increases, until an optimum is obtained. The lowest value of x for an optimum contraction could be taken as an index of the condition of the muscle. What one really determines in such an observation is the duration of stimulus above which "accommodation" comes into full play (*c.s.* p. 278),—i.e., a time which has been shown to vary definitely according to the functional condition of the muscle.

I am at present engaged in collecting material for examination on these lines. The facilities for such work are unfortunately scanty, as the apparatus is fixed in an experimental laboratory, a situation not very suitable for clinical investigations. I hope, however, in a subsequent paper to publish a full account of the clinical findings, when sufficient material has been examined.

This much can be confidently stated at the present time, that Leduc's current is far less painful than those usually employed in muscle-testing.

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**REPORT OF A CASE DEMONSTRATING PULSUS ALTERNANS,
BLOCKED AURICULAR EXTRASYSTOLES, AND ABERRANT
VENTRICULAR ELECTRIC COMPLEXES.**

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THE following case is of interest because of the presence of alternation in the pulse, the occurrence of blocked auricular extrasystoles and an aberrant type of ventricular complex in the electric curves.

History. J. H., aged forty-five years, a widower, is employed as a butler. He was admitted to University College Hospital, London, on April 1, 1911. His father is aged seventy-six years; hale and hearty. His mother died of nephritis, aged sixty years. One brother died of rheumatic fever, aged thirty-five years, another of diabetes, aged twenty-eight years, and a third, of cirrhosis of the liver, aged forty-two years. A sister died in early life of a disease unknown to the patient. Three brothers and a sister are still living and well. As a child the patient had measles; later, at the age of eight years, diphtheria. Scarlet fever, chorea, rheumatic fever and tonsillitis are denied.

When aged twenty-five years, the patient suffered from an atypical attack of pneumonia. Its duration was ten days; the fever declined by lysis and convalescence was prolonged. Ten years later the patient had an attack of severe pain in both calves. There was no fever and no joint involvement. This attack lasted eight days and he remained in bed three days. He has had repeated attacks of "influenza." The first occurred at the age of twenty-four years, the second when aged forty-one years, and the third and last attack occurred twenty months ago. Each attack lasted approximately ten days. No complications are known to have followed the first two of these attacks.

All of the symptoms relative to the patient's present condition date from the last attack. Immediately after it he experienced dyspnea on exertion, mild but persistent cough and general weakness. Attacks of palpitation were apt to occur after exertion, excitement, or gastronomic indulgences. His general health remained fair, however, and he was able to pursue his work until some months

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ago, when his symptoms became exaggerated, persistent dyspnea being the most distressing symptom. Pain was never present.

Up to two months ago the patient was a moderate drinker and smoker—one or two glasses of ale per week and three pipes daily. Since the onset of this attack he has neither drunk nor smoked. Patient denies all venereal infection. No history of syphilitic manifestations is obtainable. Bowels regular; appetite good; sleep fair.

State on Admission. The patient is a fairly well-nourished man. The mucous membranes are cyanotic. There is considerable dyspnea. The thorax is markedly rachitic.

Respiratory System. The lung-liver border in front is at the sixth rib. The lower limit of the lungs posteriorly is at the tenth thoracic vertebra. The borders alter little with respiration. The percussion note is clear over the whole chest. On auscultation, numerous sibilant and sonorous rales are heard. Over a circumscribed area 4 cm. in diameter, and situated in the third and fourth intercostal space in the midclavicular line of the right chest, numerous fine crepitations are audible. Expiration is universally prolonged.

Cardiorascular System. All palpable vessels are soft. The pulse is markedly irregular; its rate per minute is 85 to 100. The systolic blood pressure is 150 mm. Hg. The apex beat is felt in the fifth intercostal space in the midclavicular line, and is diffuse and wavy. There is no thrill. The right limit of cardiac dulness lies 4 cm., the left limit 11 cm. from the mid-sternal line. Upper limit of cardiac dulness is at the third rib. There is marked epigastric pulsation. The sounds at the apex are dull and distant. A soft systolic murmur is present. The second aortic sound is accentuated.

Abdomen. Liver, spleen, and kidneys are not palpable. No ascites present.

Extremities. There is slight edema of the lower extremities.

Nervous System. Negative.

Urine. Acid; traces of albumin; no sugar. In the sediment there are occasional granular casts, a few white blood corpuscles and amorphous urates.

Sputum. The sputum was negative for tubercle bacilli on three successive occasions.

During his stay in the hospital the patient's pulse became more regular. The systolic murmur disappeared. The edema cleared up, and the breath sounds became free of rales and crepitations. The blood pressure fell to 100 to 110 mm. Hg and stayed there. All subjective symptoms were markedly relieved.

The Polygraphic Tracings. The pulsus alternans is well shown in the accompanying tracings (Figs. 1 and 2). As is usual, when pulse alternation is combined with extrasystoles, the alternation is more marked after the premature beat. It may be noted that, as

pointed out by Windle,¹ the alternation sometimes becomes more prominent before the advent of the extrasystole (Fig. 2). The phase of respiration in which the extrasystole occurs, seems to bear no fixed and regular relationship to the degree of alternation. This relationship was present in certain of Windle's cases.

The concurrence of extrasystoles with the *pulsus alternans* so confused the radial curves that at first the case was taken for one of fibrillation of the auricles.

FIG. 1

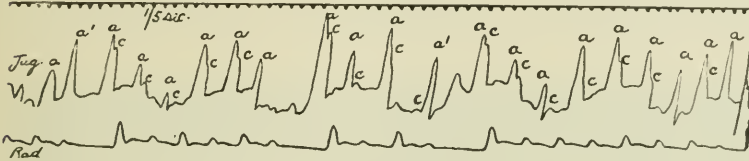
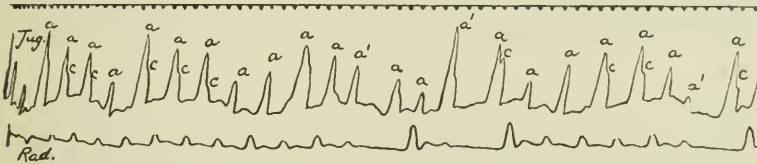


FIG. 2



FIGS. 1 and 2.—Polygraphic tracings. The radial curves show marked irregularity, as a result of auricular extrasystoles and alternation. In the jugular tracings of Figs. 1 and 2, at the points marked *a'*, peaks are seen which correspond to auricular extrasystoles. Fig. 2 shows the increase in alternation before the occurrence of the extrasystole.

The Electrocardiographic Curves. A large number of electrocardiographic curves have been taken from this patient, many with simultaneous radial curves. They are of interest from several points of view. Characteristic extrasystoles are shown in the accompanying figures. The lead in each case was from right arm to left leg.

The rhythmic beats are represented by small *P* summits, corresponding to auricular systoles; *R*, deep *S*, and *T* summits correspond to ventricular systoles. From time to time, the regular rhythm is interrupted by premature beats readily recognized as arising in the auricle. Examples are shown in Figs. 3, 4, and 6. Taking the most simple form of mechanism, such as is shown at the end of Fig. 3, and considering the last four cycles of this figure, we have first a normal beat accompanied by the usual summits. A beat of the same character follows it, but one in which *T* is deformed by a downward directed peak (*P*), representing the ectopic and premature auricular contraction.

¹ Observations of Pulsus Alternans, Heart, vol. ii, p. 95

This premature auricular contraction, represented by an anomalous complex in the electric curve, is followed by a ventricular complex of almost normal form for this patient. It differs from the usual complex only in so far as *R* is increased and *S* slightly diminished. The fourth cycle at the end of this figure represents the beat which follows the pause. It is of perfectly normal outline.

We have then, in the first instance, a clinical picture of a premature auricular contraction, represented in the electric curve by an anomalous auricular complex and a practically normal ventricular complex. The slight variation noticed in the ventricular complex is not an uncommon accompaniment of premature auricular beats,

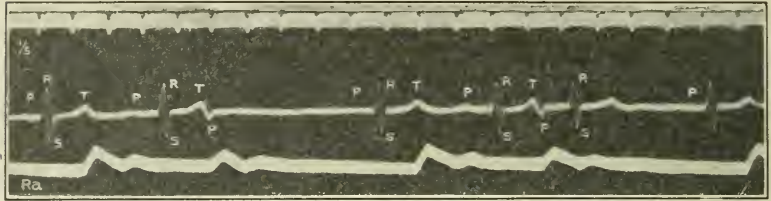


FIG. 3.—Simultaneous electrocardiographic and radial curves, showing two premature auricular contractions, the first of which gives no ventricular response. Note the small variation following the first premature auricular contraction. Similar variations are seen in Fig. 4.

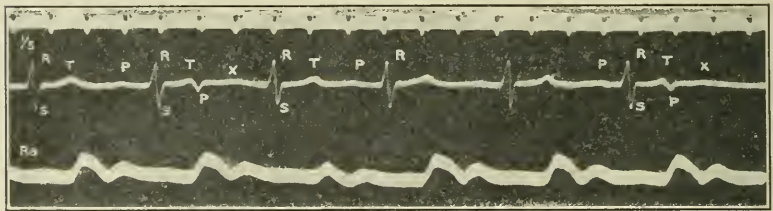


FIG. 4.—From the same case. Two premature contractions are shown. The first yields a ventricular response after an exaggerated interval; the second gives no response.

and will be further referred to in a subsequent paragraph. For the time being it may be well to notice that the *P-R* intervals corresponding to the premature contractions are rather larger than the *P-R* intervals of normal beats. But this phenomenon, the increase of the *P-R* interval accompanying normal cycles, is at times considerably exaggerated; a curious example is shown in Fig. 4, where the *P-R* interval for the first abnormal cycle is increased to $\frac{2}{5}$ seconds. The increase is so great that the corresponding ventricular complex, instead of falling prematurely, falls at the expected point. This phenomena is seen in rather an exaggerated form in the arterial curve accompanying the electrocardiogram. The radial up-stroke accompanying the abnormal cycle falls late and is small.

Further exaggeration of the *P-R* interval is not found. The next stage is marked by the presence of blocked beats. One of these is shown at the beginning of Fig. 3, another at the end of Fig. 4.

The premature auricular contraction is clearly recognized in the electric curves by the deformity it produces in the *T* wave with which it is synchronous. It is followed by no ventricular complex, but is succeeded by a summit which has hitherto received no description. If the long pause succeeding the blocked auricular contraction is carefully examined, a small and low summit marked *X* will be found, the apex of which falls at a distance of one and three-fifths seconds, after the abnormal auricular complex. This summit

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FIG. 5.—From a different case. An electrocardiogram showing two premature auricular contractions, the second of which is blocked.

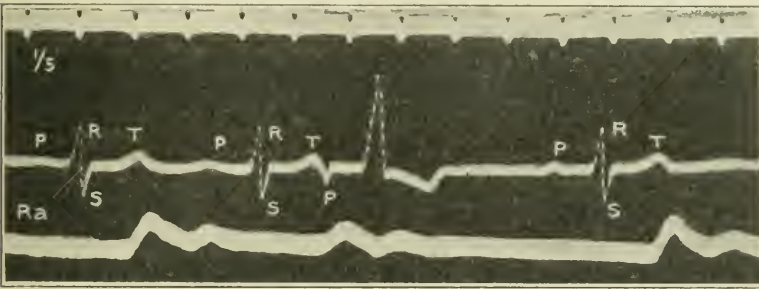


FIG. 6.—From the same case as Figs. 1 to 4. An electrocardiogram showing a single premature auricular contraction. The ventricular response is accompanied by an aberrant ventricular complex.

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is found regularly after all blocked premature auricular contractions in the curves from this patient, and appears to be associated with the abnormal auricular contraction. The same wave is seen after the first premature auricular contraction of Fig. 4. It is not found in any other position in the curves.

Blocked premature auricular beats have been previously described by Hewlett² and Lewis.³ A new curve is published from the patient described by the latter, and is shown in Fig. 5. This figure shows a normal cycle, of which the *T* summit is deformed by a downwardly directed peak at its opening phase. This is the rep-

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² The Blocking of Auricular Extrasystoles, Jour. Amer. Med. Assoc., vol. xlviii, No. 19, p. 1597.

³ Paroxysmal Tachycardia the Result of Ectopic Impulse Formation, Heart, vol. i, p. 261.

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representative of the abnormal auricular contraction. It is followed after a rather prolonged *P-R* interval by a premature ventricular complex of normal outline. The pause following this is succeeded by two normal cycles. The *T* summit of the last cycle is deformed by a premature auricular contraction, and this impulse is blocked and is followed by a long pause of four-fifths of a second.

It has been said that in the patient who forms the basis of this paper, the ventricular complexes corresponding to premature contractions arising in the auricle are usually of approximately normal outline. And it has been said that the deviations consist in a slight increase in the summits *R* as compared with normal beats. This increase is well shown in Fig. 3. At rare intervals the same patient showed a striking form of "aberrant" beat,⁴ an instance of which is given in Fig. 6. There can be no question that this aberrant complex (Fig. 6) is in reality the representative of a ventricular contraction of supraventricular origin. It is another example of the phenomenon described by Lewis,⁵ and it is of peculiar interest in that it shows relationships of a precisely similar nature to those described by this writer. Thus, it occurs in a case in which conduction disturbances in the junctional tissue are clearly marked and readily demonstrated. It is noteworthy that both in the original description of the phenomenon and in the case here described, blocked premature auricular contractions were present. The other point of interest is the fact that the aberrant type of response is the response which occurs soonest after the preceding ventricular contraction. Thus, comparing the two premature auricular contractions of Fig. 3 and the premature contraction of Fig. 6, the ventricular complex accompanying the former stands at a distance of two and two-fifths seconds from the preceding ventricular complex, while the aberrant complex of Fig. 6 stands at a distance of two-fifths seconds from the preceding auricular contraction. Thus, aberration appears when the pause preceding the beat in which it is shown is shortest and when the rest is shortest.

The interpretation which has been adopted in explanation of these phenomena of aberration is confirmed by the present findings. The patient now recorded presents aberrant complexes, and these aberrant complexes are closely associated with conduction changes in the junctional tissues. Moreover, the degree of aberration is apparently dependent upon the relative lack of rest which the junctional tissues experience in an individual instance. It is upon the occurrence of these phenomena that the view is based, that the anomalous ventricular complexes are dependent upon conduction defects in individual branches of the arborization. Considering the

⁴ A term which is fully explained by Lewis in "The Mechanism of the Heart Beat," London, 1911.

⁵ On the Electrocardiographic Curve, etc., Heart, vol. ii, p. 23.

ventricular complexes accompanying premature contractions in this patient, it is evident that each results from a supra-ventricular impulse, an impulse which has come down through the main bundle and which has spread through the two chief divisions of the bundle and the arborization on each side. Under ordinary circumstances, impulses travelling in this manner may be expected to and do give rise to contractions of the ventricle which yield normal ventricular complexes. It is difficult to see how the deformity of the ventricular complexes in this patient is produced, unless the impulses which give rise to them have followed an abnormal course after reaching the ventricle. In the example shown in Fig. 6, the complex closely resembles a premature contraction arising in the right or basal portion of the ventricle, and it may be suggested that the main defect, in the conduction of the impulse which produces this beat, is in the left branch of the bundle or its branches. Curves of this form have been shown to arise when the left branch of the bundle is cut experimentally.⁶

The observations upon which this paper is based, were carried out in Dr. Thomas Lewis' department, at the University College Medical School, and I have to thank Dr. Lewis for permission to record this case, as well as for invaluable aid in preparing the manuscript.

⁶ Eppinger and Rothberger. Ueber der Folgen der Durchschneidung der Tawara'schen Schenkel der Reizleitungssystem, Zeitschrift f. klin. Med., vol. lxx

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AUTHOR'S FINAL PROOF OF SECTION

FOURTH REPORT
OF THE
WELLCOME
TROPICAL RESEARCH LABORATORIES
AT THE
GORDON MEMORIAL COLLEGE
KHARTOUM
VOLUME A.—Medical

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Pathologie Exotique and American Society
of Tropical Medicine; Medical Officer
of Health, Khartoum; etc.

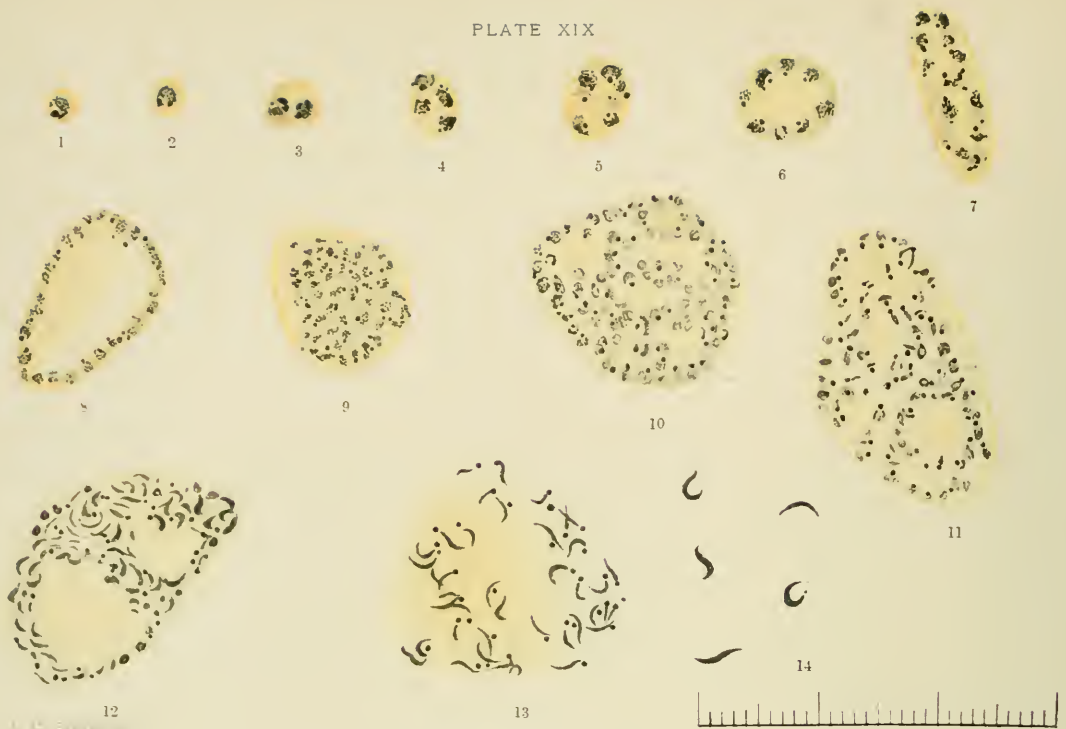
COCCIDIOSIS OF THE INTESTINE IN THE GOAT
AND
A FEW NOTES ON THE PROTOZOA PARASITIC IN
BUFO REGULARIS IN KHARTOUM
BY

A. C. STEVENSON, M.B., M.R.C.S., L.R.C.P. (LOND.), D.P.H. (CANTAB.)

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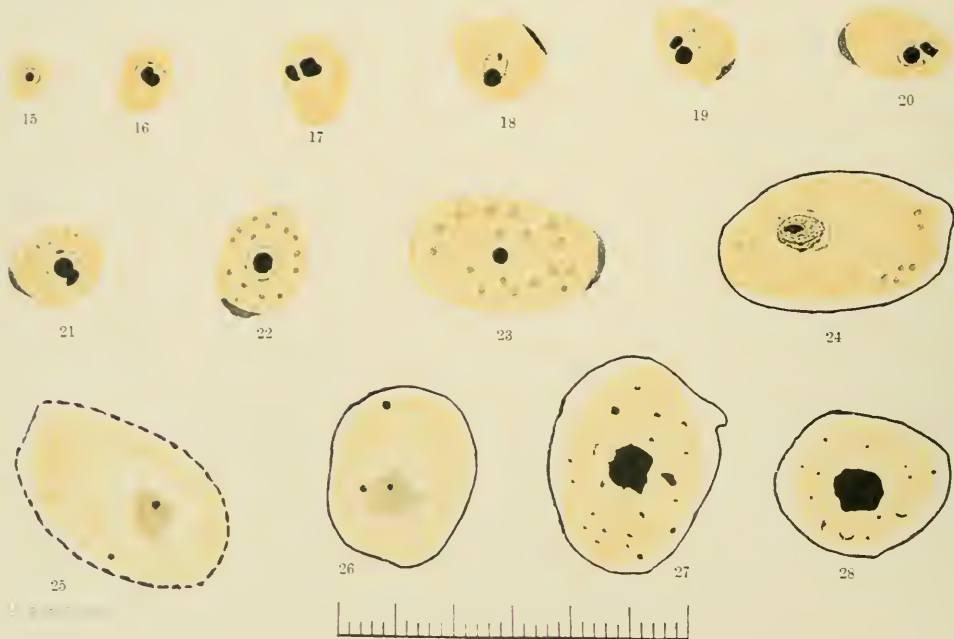


MICROGAMETE FORMATION

Scale = 30 μ

- 1-3. Early forms of microgametocyte showing division of karyosome
- 4-9. Gradually enlarging forms with repeated division of nucleus and karyosome
10. Commencing condensation of chromatin granules
- 11-12. Lengthening out of condensed chromatin to form body of microgamete
13. Adult microgametes with karyosome still apparent
14. Free microgametes with terminal flagellum

Iron Hematoxylin and Orange Stain



Scale = 30 μ

MACROGAMETE FORMATION

- 15-17. Early forms showing primary division of chromatin of nucleus
18. Cap of extruded chromatin seen flattened between parasite and containing cell
- 19-21. Secondary division of chromatin of nucleus
- 22-23. Commencing formation of granules in protoplasm after nuclear division
- 24-26. Adult macrogametes awaiting fertilisation. In 25 capsule is not yet completed
- 27-28. After fertilisation showing irregular chromatin staining granules in cytoplasm

Iron Hematoxylin and Orange Stain

COCCIDIOSIS OF THE INTESTINE IN THE GOAT

BY

A. C. STEVENSON, M.B., M.R.C.S., L.R.C.P. (LOND.), D.P.H. (CANTAB.)

While working in the Wellcome Tropical Research Laboratories at Khartoum in the winter of 1908-9, I came across the above condition. The goat was one that had come from higher up the Nile and had been sent to the laboratories for diagnosis. Dr. Balfour was away, and, unluckily, notice was not given me of the goat's death till well on in the day, so that the post mortem took place about 9 hours after death and in the afternoon. The goat, I learnt, had had great difficulty over defæcation, though from the condition of its stomach it was feeding well.

Post mortem.—Skin very scaly, condition resembling favus. Thoracic organs normal, liver, spleen, kidneys, etc., normal. A fair amount of fluid in the peritoneal cavity, with adhesions recent and old. Numerous encysted cysticerci present in outer wall of gut, some calcareous. The upper part of the small intestine was very translucent, and showed numerous small white patches varying from 1-3 mm. in diameter. Portions of the gut with nodules were hardened in formalin and showed coccidia in the later stages of sporogony, the capsule being formed, and many microgametes free. The intestinal epithelium was practically non-existent, but most of this was probably due to post mortem changes. Loss of intestinal epithelium

The second goat was one that also seemed ill, and, externally and internally, the conditions were much the same as in the first, except that the colonies in the gut were fewer in number, and the gut in this case was not denuded of its epithelium. Here sporogony had not gone so far, the coccidia seldom having capsules, but the growth of gametocytes was well shown. Tissue was fixed in corrosive sublimate and glacial acetic acid.

The third goat was a younger one, and did not show any marked signs of illness. The condition of favus was not so marked, and the colonies of coccidia were again fewer in number. Here again, however, only early sporogony phases were to be found, and those mostly microgametocytes. The mucous membrane was intact.

The colonies of coccidia are very well defined, very few individuals being found infecting cells away from the main mass. So definite is this that the cells on one side of the lumen of a gland may be infected while those on the other are not. Clearly defined distribution of the coccidia

I have later received from Dr. Balfour portions of the intestines of two other goats, and also their fæces. The first of these, Dr. Balfour tells me, was distinctly ill, the second, however, showed no symptoms. In both of these, coccidia were present, but only in late stages, many having their capsules formed. The mucous membrane of the small intestine was in both cases entirely gone, though in the portions of large intestine examined it was still present. There were also some enlarged lymphoid follicles with formation of scar tissue in the centre, and in the large intestine under the mucous membrane there were small round cell masses, each containing a small nematode worm. The lymphoid patches in the small intestine closely resembled those in a human case from which Dr. Balfour sent me tissue some time ago. Search for coccidia in the fæces was disappointing. Very few were found and those that were found showed no signs of division, being practically in the same state of development as the later stages seen in sections of the intestine.

SCHIZOGONY CYCLE

No coccidia in this stage of development have been found in any of the tissues. Professor Minchin suggests that this stage takes place before any symptoms are seen in the animal. From what I learn from Dr. Balfour, the second of the goats, of which portions of the intestines and the fæces were sent home to me, appeared perfectly well, though the coccidia were far advanced in development in the sporogony stage.

It would appear, however, that there is a schizogony of a double type, *i.e.* that at a very early stage there is a differentiation of sex amongst the merozoites and that we get macro- and micro-merozoites going on through several generations.

I am led to this belief by the fact that in any one colony in the gut there is always a great excess of one sex, and in several colonies I have found nothing but microgametocytes, those nearer the lumen of the gut being older than those in the deeper portions of the glands.

Further, I find that in sections of liver from a rabbit infected with coccidiosis, there are unquestionably two types of schizonts present. The one produces large merozoites with a well-marked nucleus showing a well-marked karyosome, closely resembling the young macrogametocyte described on page 358. The other type of schizont divides into small merozoites which are more numerous than the above, and which have a nucleus with a small karyosome and numerous small granules of chromatin as in the young microgametocytes described later. This double schizogony has been described in *Adelea ovata*.

SPOROLOGY CYCLE

Microgamete Formation (Plate XIX., figs. 1-14)

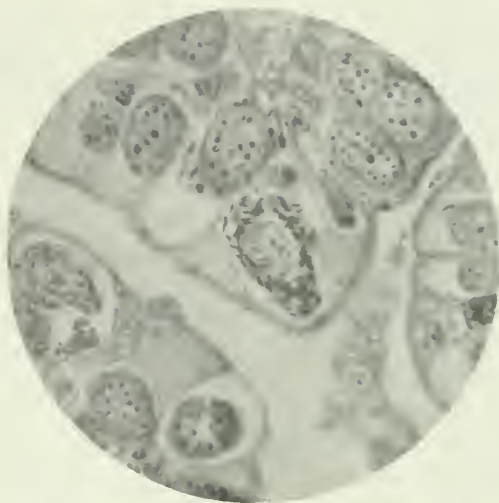
The microgametocyte is first seen in the cell as a small body about $3-4\mu$ in diameter, with an indefinitely outlined nucleus containing small granules of chromatin and one larger one, the karyosome, generally a little separated from the others, which are arranged in a crescentic manner on one side of it. The karyosome divides first and this is followed by the division of the remainder of the nucleus. Frequently, division is more rapid, the karyosome dividing twice before division of the rest of the nucleus takes place. Concurrently with this the protoplasm of the microgametocyte increases in amount. Division goes rapidly on, the nuclei arranging themselves around the periphery of the microgametocyte until a large body is formed often 30μ in the longest diameter, and the number of nuclei is often so great that the surface becomes involuted to accommodate them all. The size of the adult microgametocyte, and the number of nuclei present in it, vary considerably at the time the final changes begin to take place. The only apparent reason for this irregularity seems to be the varying amount of pressure exercised by the surrounding tissue and parasites.

When division of the nuclei has stopped, the small granules of chromatin in each nucleus condense into a small ovoid body with the karyosome slightly separated from it at one pole. This arrangement of the karyosome is much better seen in sections stained by Twort's or Giemsa's stain, than in those stained by iron hæmatoxylin (Plate XIX., fig. 13, and Plate XX., fig. 4). These ovoid bodies gradually lengthen out into thin spindle shapes, and are all arranged round the mass or masses of residual protoplasm. Whether there is one centre or more depends on the frequency of division of the nuclei of the microgametocyte and the subsequent involution of the surface.

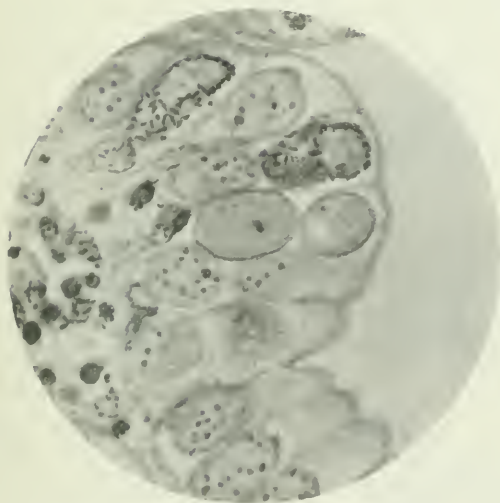
The adult microgamete has a terminal flagellum and a vacuole situated about a third of its length from the one end of the body. The karyosome seems to disappear, but may possibly reappear as the flagellum. I have only seen the vacuole definitely in the tissue lately sent home by Dr. Balfour, and even there it does not appear readily



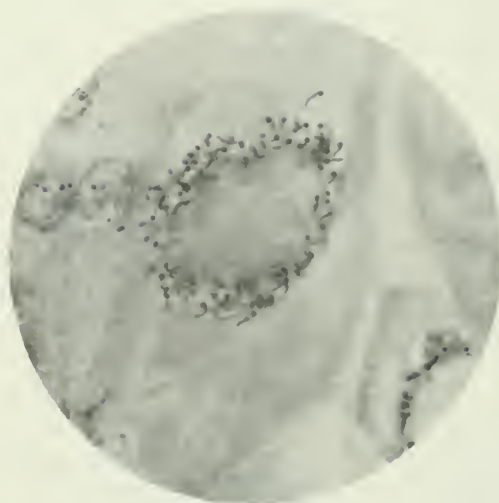
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COCCIDIOSIS OF INTESTINE IN GOAT

1. Portion of villus with nearly every cell infected. On the right, young macrogametocytes with two young microgametocytes about centre. On the left, nearly adult macrogametocytes.
2. Macrogametocytes and one microgametocyte with nearly adult microgametes in centre.
3. Two microgametocytes showing arrangement of microgametes around two centres of residual protoplasm. Also two macrogametocytes with cyst already formed round them while still in host cell, evidently before fertilisation as karyosome is still present.
4. Nearly adult microgametes showing karyosome still attached to one end.

Photographed with Zeiss 2 mm. lens and camera length of 50 cm. Figs. 1, 2 and 3 with No. 4 compensating ocular and fig. 4 with No. 5 compensating ocular.

with iron hæmatoxylin staining. It was best observed by staining with Ehrlich's hæmatoxylin and eosin (fixation various). As my drawings were finished before I received this last tissue, the vacuole is not shown.

Macrogamete Formation (Plate XLX., figs. 15-28)

The youngest form of the macrogametocyte observed is considerably larger than that of the microgametocyte, being $5\mu-6\mu$ in its longest diameter, and the protoplasm stains more readily with acid stains than that of the microgametocyte. The nucleus has a marked karyosome, but except in the earliest stages there is very little other chromatin present. A very interesting peculiarity of the chromatin in the macrogametocyte is that it seems impossible, in tissue fixed in corrosive sublimate and glacial acetic acid, to stain it with basic dyes, such as the blue in Giemsa's stain and the neutral red in Twort's stain, though it stains readily with iron hæmatoxylin (Heidenhain). The chromatin in the microgametocyte is readily stained by the basic stain in these two preparations.

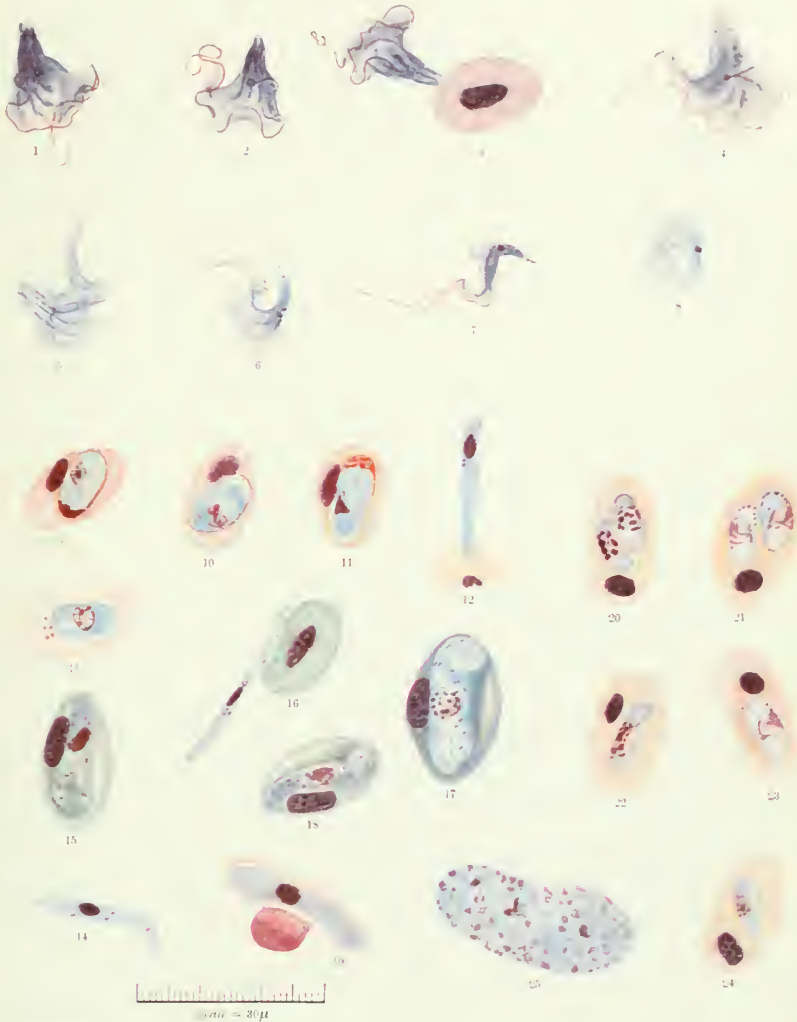
The karyosome at any early stage divides, and one-half is extruded from the cell nucleus and cell, and is often seen as a cap of chromatin flattened out between the parasite and its containing cell, while the remaining portion divides again. The one part of this is again extruded or absorbed, while the remainder persists as the karyosome of the adult macrogamete.

The macrogametocyte enlarges, and, soon after the second division of the karyosome, granules appear in the protoplasm, at first small but eventually growing much larger. These granules retain iron hæmatoxylin stain well, though not so markedly as the karyosome. They stain deeply with the acid stain in Giemsa and Twort.

Enlargement to full size, $26\mu-28\mu \times 17\mu-18\mu$, goes on without much further change, except that the nucleus becomes enlarged and vesicular with the single marked karyosome remaining. The granules in the protoplasm also become larger and more marked, when nearly adult capsule formation commences. Granules are secreted which stain readily with iron hæmatoxylin, much less readily with Delafield or ordinary hæmatoxylin, and not at all with either the basic or acid stains in Giemsa or Twort. These granules arrange themselves round the periphery of the macrogamete, appear to be extruded and then to flatten out on the outside of the parasite, openings being left between the various plaques thus formed which fuse at first in places, then altogether except for one opening left at one end of the long diameter of the cyst wall to form a micropyle. A cone of attraction appears at one end of the parasite which is directed towards the opening in the cyst.

Fertilisation apparently takes place at this stage from the change in the character of the nucleus, though I have been unable to find direct proof of the entrance of the microgamete. In the apparently unfertilised macrogamete, the nucleus possesses but little chromatin besides the karyosome, whilst, apparently after fertilisation, the whole nucleus becomes a dense mass, staining strongly with iron hæmatoxylin and irregular in outline. At this stage, too, there are seen in the protoplasm numerous small irregular masses staining like chromatin. Are these portions of the karyosome expelled from the nucleus as described by Schaudinn, or are they remains of numerous microgametes which have entered the macrogamete and become degenerate as described by the same observer in *Cyrtospora caryolytica* in the mole, which this coccidium seems closely to resemble in its sexual development? There is no definite evidence.

As mentioned above, I have not been able to follow the matter further, and so have no knowledge of the number of spores or sporozoites formed. All that I have seen in examining the faeces are a few coccidia in the same stage of development as the most advanced of those in the intestinal mucous membrane.



PROTEZ A IN BLOOD OF *Buteo vulgaris*

1-8. *Trypanosoma rotatorium*. 1-3 show the rilled-up condition of large forms, the shape usually seen in fresh specimens. 4 and 5 show unrilled forms, 5 shows arrangement of myonemes. 6-8 show small forms.

9-14. *Hemogregarina tuuiscensis*. 9-13 show space in capsule which stains red with Romanowsky stain and black with Iron Hematoxylin.

15-19. *Drepanidium magnus*.

20-25. HEMOGEGARINES IN THE BLOOD OF *Triphyrus nilei*. 25 is possibly a schizont form from the lung.

Giemsa Stain. The green of the blood corpuscles in figs. 15-18 is due to over fixation in osmic vapour.

PATHOGENICITY

Coccidiosis in the intestine of cattle, goats, etc., has been described in Central Europe. There, however, it was seldom fatal except in young animals. I have now considerable doubt, however, whether the coccidia will account for the illness of some of these goats. The stripping of the entire mucous membrane of the small intestine to the very depth of the glands, except in those places where coccidia are, the enlargement of the mesenteric glands, which show marked increase of fibrous tissue and centres of cell degeneration, and the fact that advanced stages of coccidiosis give no symptoms, seem to point to some more acute cause than coccidiosis, unless there is the formation of some virulent toxin.

I regret I have not enough data to definitely place the organism. It is probably the same as that affecting cattle in East Africa, as I have lately heard, and possibly the same as that in Central Europe. As mentioned on *page* 358, its sexual development seems closely allied to that in the intestine of the mole, though its habitat is not in the nucleus.

A FEW NOTES ON THE PROTOZOA PARASITIC IN BUFO REGULARIS
IN KHARTOUM

BY

A. C. STEVENSON, M.B., M.R.C.S., L.R.C.P. (LOND.), D.P.H. (CANTAB.)

PROTOZOA IN THE BLOOD

Trypanosoma rotatorium

In examining fresh specimens of the above toad's blood in Khartoum, I found *Trypanosoma rotatorium* present, without extensive search or cultivation in each instance, in 6 cases out of 21. The period of examination was from the middle of November to the middle of February.

I had at first considerable difficulty in recognising the organism in the fresh state, as in that condition its appearance when adult is quite different from that seen under similar circumstances when search for the commoner mammalian trypanosomes is made.

The trypanosome is seen as a small body, roughly about the same length in longest diameter as the red blood corpuscle, resembling the flower of the convolvulus in shape, and rapidly rotating on its long axis. Its flagellum can be seen flickering beyond what would be the edge of the petals of the flower. The posterior end of the parasite, or what would be the base or narrow end of the flower, is generally applied to one of the red blood corpuscles. Though I know this was the first trypanosome described, I have never seen or heard mentioned the reason of the name.

By emulsifying blood in citrate of soda solution, fixing with osmic acid vapour, spreading gently with a needle and drying, I was able to stain the parasite in this condition (Plate XXI., figs. 1-3). Spreading films in the ordinary way generally leads to their being unrolled or crushed.

An interesting point which appears in some of the unrolled and stained specimens is the arrangement of the myonemes. Each myoneme appears to start from near the posterior end of the body, about half-way to the edge of the undulating membrane, to which they radiate, each divides into two, and each half coalesces with the half from the myoneme on each side of it, except in the case of the first and last, where the anterior and posterior halves of each respectively remain alone (Plate XXI., fig. 5).

Pathogenicity
is doubtfulMethod of
making and
fixing filmsArrangement
of the
myonemes

From this arrangement a stimulus started in one myoneme may be transferred to the next, and thus undulatory movement of the membrane may be kept up.

HEMOGREGARINÆ

Two forms occur very commonly in this toad. One form or both were present in 17 out of 21 cases. The period of examination was the same as above. They were both far more common in the blood in the earlier part of my stay in Khartoum than in the latter, and as I never found any signs of schizogony in any of the organs, I think it is a fair assumption that this process only takes place in the summer months in cold-blooded vertebrates. I believe that the schizogony stages of similar parasites in lizards found by Dr. Wenyon were in specimens collected in the warmer part of the year. These stages in warm-blooded animals, the jerboa for instance, seem to take place all the year round.

The first, and if anything the commoner form of these two hæmogregarines, is found in the blood corpuscle in a firm cyst wall, and is sharply bent upon itself about the middle. The cyst wall is double at the end at which the parasite is bent, and the space between the two layers contains a substance which stains a bright red with Romanowsky stains and retains the iron hæmatoxylin stain well (Plate XXI., figs. 9-11 and 13). The cyst is not as long as the blood corpuscle. Observed in citrated blood, or in a similar emulsion of spleen pulp the parasite, especially in the latter situation, is often seen free (Plate XXI., figs. 12 and 14). Its movements are fairly rapid, and of a definite gregarine type, contractile waves passing down the body being seldom seen until motion has practically ceased. When the motion begins to slow down, the mucoid thread secreted by the organisms becomes visible, and, after forward motion ceases, this thread has been seen to become corkscrew-shaped. Movement has also been seen in the cyst, the parasite completely turning round inside it. Average size of the cyst is $14\mu \times 8.8\mu$.

This parasite is probably the same as that observed in a frog in Tunis, and has been named *Hæmogregarina tunisiensis*.

The second and larger hæmogregarine is probably *Drepanidium magnum* (Plate XXI., figs. 15-19). It lies apparently free in the blood corpuscle, of which it fills the entire length, its two ends being slightly bent over. Size in corpuscle $23\mu \times 7\mu$. In films in which the blood corpuscle has disappeared a stained capsule is visible, and, in citrated blood, the ends of the organism are generally still bent as if enclosed. I have never seen this form actually motile, but possibly the large free organism shown (Plate XXI., fig. 18) is of this type. Both forms show a marked rostrum.

On staining tissue fixed with saturated corrosive sublimate and glacial acetic acid, the nucleus of both these hæmogregarines is found to be that of the definite gregarine type mentioned by Professor Minchin, e.g. a vesicular nucleus containing granules of chromatin on the fibres of a fine network. In these cases there are smaller granules round the periphery with generally four larger granules in the centre.

I have shown in the drawing some hæmogregarines from the river turtle (*Trionyx*) of the Nile (Plate XXI., figs. 20-25). The specimen was a young one. I also show a possible schizogony stage of this from a film from the lung (Plate XXI., fig. 25), but as it was the only one I found, I do not place much reliance on it, and, in addition, the films were hurriedly made.

PROTOZOA IN INTESTINE

Flagellates

Trichomonas and *Hexamitus* (*Octomitus*) are seen very commonly in most cases (Fig. 107). They show no difference from those described by Dobell in the frog in this country or from those described in the mouse and rat by Wenyon, where I have also observed them.

Hæmogregarina tunisiensis

Drepanidium magnum

Flagellates



Ciliates

Nyctotherus cordiformis and a *Balanidium* are both common, but instead of *Opalina* we have another organism something of the same class though it differs in its nuclear arrangement. The largest specimens of this are about 80μ by 60μ , while the smallest are



about 60μ by 16μ . They are covered by cilia of a uniform length, have no apparatus for ingestion or egestion, and the nucleus usually consists of two pear-shaped bodies connected by a definite narrow strand (Fig. 108). Up to the present I have not identified this. It is characterised by having a definite spine at one end, especially in the smallest and middle-sized forms.

I cannot conclude without expressing my deep thanks for the help and kindness I received from Dr. Balfour, Mr. Currie, and any official of the Sudan Government, from the Sirdar downwards, with whom I came in contact.

PECULIAR BODIES FOUND IN THE INTESTINAL LYMPHOID FOLLICLES
OF AN EGYPTIAN

BY

A. C. STEVENSON, M.B., M.R.C.S., L.R.C.P. (LOND.), D.P.H. (CANTAB.)

(Plate XXII., figs. 2-6)

This plate is to illustrate peculiar bodies found in the solitary lymphoid follicles of the small intestine of a man, an Egyptian, who died suddenly in Khartoum. The tissue was sent home to me by Dr. Balfour on the chance of the case being one of coccidiosis of the intestine, the macroscopic appearance being practically the same as that seen in coccidiosis of the goat's intestine which we had observed shortly before, and which is described elsewhere (*vide page 355*).

On section the epithelial cells of the mucous membrane were found to be practically destroyed, only a few cells, and those degenerate, being seen in the depths of the glands. How much of this was due to post mortem changes I cannot estimate. In the sub-epithelial layers of the villi, there seems an excess of cellular elements which are either very degenerate or possibly parasitic. Stained by iron hæmatoxylin and orange the majority of these cells show an indefinite unstained nucleus with one or more small chromatin dots; the few remaining cells stain normally so far as the nucleus is concerned. If parasitic they are possibly amœbæ (? histolytica), but I am more inclined to think them degenerate tissue cells.

At the periphery of the lymphoid follicles and at their base are the masses illustrated (Plate XXII., figs. 2 and 4). They are large cells, probably the endothelial cells of the lymph spaces, swollen up so as to occupy practically the whole lumen, and packed with small round and oval bodies of about $1\text{--}5\mu$ in longest diameter. These small bodies, when stained as mentioned above, are greenish in colour, generally show a black dot in their substance and the larger of them are usually situated nearer the centre of the mass than the smaller. Larger bodies of the same staining reactions were also seen in cells but were few in number (Plate XXII., fig. 3). Stained by Giemsa, the stain being used in the same method as Twort's for *Entamoeba coli*, the clusters of small bodies are a bluish-purple while the ordinary nuclei are greenish-blue and the rest of the tissue pink.

Position of
the masses

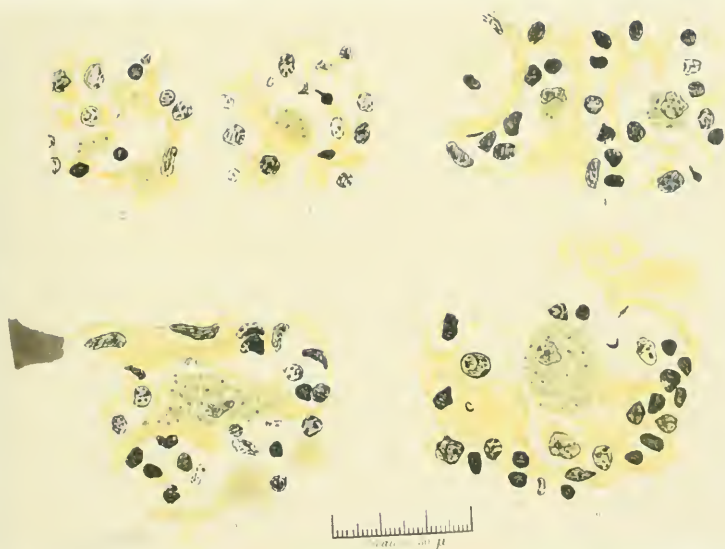
Bacilli were seen in only one or two sections stained by Twort's stain. They were scattered and of large size, resembling those seen in much post mortem tissue in Khartoum. Tubercle bacilli were examined for but not found.

What is the nature of these bodies? Are they parasitic or are they massed in the cells by phagocytosis? I do not think they can be remains of the dead cells in the sub-epithelial layers as they stain absolutely differently with Giemsa, but on the other hand their colour by iron hæmatoxylin and orange closely resembles that of degenerative blood corpuscles in cells.

I have not found any of the larger bodies in the Giemsa-stained sections, so cannot say what their staining reaction is, but their presence certainly might suggest a parasitic origin for the smaller.

Since writing the above, I have found some very similar masses of bodies in similar situations in the stomach of a mouse which was in apparently good health.

PLATE XXII



PECULIAR BODIES FOUND IN THE INTESTINAL LYMPHOID FOLLICLES OF AN EGYPTIAN

Drawings of portions of sections stained with Iron Haematoxylin and Orange

2 & 4. Small and medium-sized bodies in portions of cells

3. Large body lying apparently free in lymph space

5 & 6. Endothelial cells in lymph space packed with bodies of varying size

IRREGULARITY OF THE HEART'S ACTION IN HORSES AND ITS RELATIONSHIP TO FIBRILLATION OF THE AURICLES IN EXPERIMENT AND TO COMPLETE IRREGULARITY OF THE HUMAN HEART.

By THOMAS LEWIS.*

(From the Cardiographic Department, University College Hospital
Medical School).

TOWARDS the termination of the observations made upon complete irregularity of the heart's action in the human subject, a full report of which was published in *Heart* in March, 1910, it occurred to me that if I could find a similar pathological affection in any of the lower animals, it might finally settle the nature of the irregularity with which I had to deal.

My clinical observations and my experiments all pointed in one direction, and I felt confident that the disorder of the ventricular movements was in reality the outcome of fibrillation of the auricles. The discovery of a similar irregularity in one of the lower mammalia would provide an opportunity of putting the matter to a direct test, for an animal so affected might be opened and the heart inspected as it beat *in situ*.

My attention was directed especially to the domesticated animals, for they have a similar environment to man and are under observation and control. I first thought of the dog, and made a number of enquiries in regard to the pathological mechanism of the heart in this animal, but eventually abandoned the search because of the marked respiratory arrhythmia which the dog exhibits. I had no hope of obtaining the material I required from this source, if it exists, for on account of its obvious rarity and the presence of the natural arrhythmia, I could neither collect it myself, nor rely upon the observations of others in identifying the irregularity sought.

Horses became the next subjects of search. The relative frequency with which these animals are vetted, and the regularity of the heart's action in horses suggested that they might be a suitable hunting ground; and I was encouraged by the description in several veterinary text books of a rare affection of the horse's heart under the term "tumultuous action of the heart." But I should not have been successful had it not been for the great kindness of Professor Woodruff of the Royal Veterinary College, and for that of Major-General F. Smith, who was then chief of the Royal Army Veterinary Corps. While Professor Woodruff arranged that a careful

* Working under the tenure of a Beit Memorial Research Fellowship.

search should be made amongst horses attending the out-patient department at the Veterinary College, General Smith very kindly sent circulars of enquiry to the various dépôts under his command. I was able to interest a number of other veterinary men, both in London and the provinces. In this manner a very large number of animals came under observation from the required point of view ; and, although the affection is of great rarity in horses, I have been fortunate enough to collect notes and observations upon five animals. These notes and observations are by no means complete. The difficulties connected with such work are considerable. It has to be carried out in places ill suited to it and observations are often hampered by the prejudice of the owner or by official restrictions. Nevertheless, the material which has been gathered seems of sufficient interest and importance to permit its publication in detail at the present time.

Horse 1. This animal was seen at Colchester through the courtesy of General Smith. It was a gelding cob of 15 hands $3\frac{1}{2}$ inches. The age was nine years. The horse had come under observation seven months previously, when it showed symptoms which prevented it from working. Irregularity of the heart's action was noted ; when galloped a hundred yards the animal became acutely distressed, foaming at the mouth occurred, the breathing became laboured and eventually the animal staggered and fell. At times there was hæmorrhage from the nostrils. A large pulsation at the root of the neck and in the neck itself had been noted, and this was stated to be increased by exertion. There was rarely, if ever, any cyanosis. The arterial pulse was usually counted at 14-16 beats per minute.*

The animal was examined in its stable at Colchester on December the 4th, 1909. The pulse, which was palpable in the superficial temporal and submaxillary arteries, was feeble. Its rate lay between 20 and 50 per minute, varying very considerably from time to time. It was absolutely irregular in force and in rhythm. Sometimes a long pause was felt, sometimes a run of a few quick beats ; at other times beats of very varying lengths followed each other irregularly. The pulse rate increased markedly (from 40 to 90 beats per minute) with light exercise. At the root of the neck pulsation of a general welling character was visible and it could be followed along the external jugular veins as far as the middle of the neck. It was easily palpable with the finger, and the veins in which it occurred were obviously distended. The pulsation was synchronous with the arterial pulsation, but slightly more frequent in its incidence. The heart was auscultated and the irregularity in its characteristic form could be clearly identified. The first and second heart sounds seemed clear, no adventitious sounds were audible. There was no cyanosis, but there was dropsy. The legs were puffy and the most dependent portions of the belly pitted very readily on pressure. A great deal of time was spent in attempts to obtain

* The normal rate is 35-40 beats per minute.

graphic records of the movements, but they were only partially successful. Simultaneous records were out of the question, on account of the restiveness of the animal. A few arterial and venous curves were obtained separately.

A short strip of arterial curve taken from the superficial temporal artery is shown in Fig. 1. The rate for the six beats shown is 43, and the beats have respective lengths, in fifths of seconds, of 10, 5, 6.3, 4.7, 6.4 and 9.0. Another strip in my possession shows beats in fifths of seconds as follows :—7.5, 11.8, 6.5, 9.2, 4.2, 11.2, 6.4, 7.4, 7.8, 6.0, 4.4, 15.7, 6.2, 7.8, 7.6, 13.3 6.3, 7.7, 13.7 ; an average rate of 32 beats per minute.

Strips of the venous pulsation in the external jugulars are shown in Fig. 2, 3 and 4. The pulsation was carefully timed subjectively, and the sharp upstroke ending in a pointed peak synchronised with the arterial pulsation. At times a beat was recorded from the veins when no pulsation in the artery was felt. The tracings of the venous pulsations are of the characteristic plateau form and during the diastole, where this is long, a stasis wave is seen and there are fine oscillations upon it, (especially well seen in the long pause of Fig. 3 and 4).

The animal was shot and a post-mortem was made. The pericardium was thickened and enveloped in fat. The mitral and tricuspid valves seemed a little thickened. The muscle of the ventricles was thick and friable. There were some large patches of fibrosis in the left auricle. The lungs, abdominal viscera and arteries appeared normal. The heart was sent to Dr. Cohn of New York.

Horse 2. The following notes are abstracted from a War Office report. The animal was 16 years of age and had seen 9 years service in the South Wales Borderers. It had been under observation for some while for poor condition and wasting ; until 4 days before admission it had worked satisfactorily. It was brought to the sick lines on December the 28th, 1909, having refused its food. The pulse was counted at between 80 and 90. The temperature was 105.2° Fahr.* The respiration was hurried, 25 to the minute,† and there was evidence of pain, the animal looking continually round to the side. The horse refused food and water. Regurgitation through the jugulars was extraordinarily conspicuous, and quite apparent from the other end of the loose box in which it was stalled. On palpation it resembled an arterial pulse, so vigorous and strong was the beat. Congestion of the visible mucous membranes was present, but only slightly, and this probably by reason of the anæmic condition of the animal. Pain was manifested on manipulation of the cardiac area. Auscultation of the heart revealed a confused, irregular and excessive action of the heart.

Treatment was expectant. Mustard was applied over the ribs of the cardiac region. On the 29th the high temperature was maintained and the

* The normal temperature of the horse is 100.4-100.9° Fahr. .

† The normal respiratory rate is 8-10 per minute.

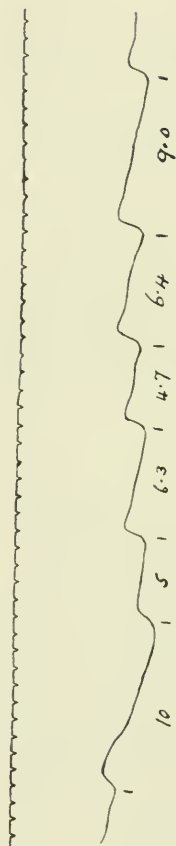


FIG. 1.

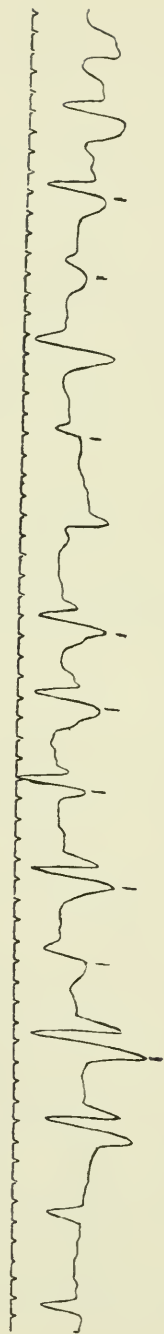


FIG. 2.

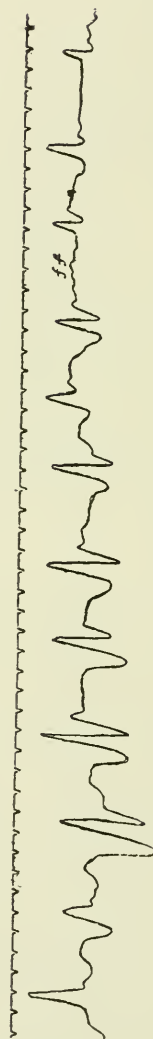


FIG. 3.

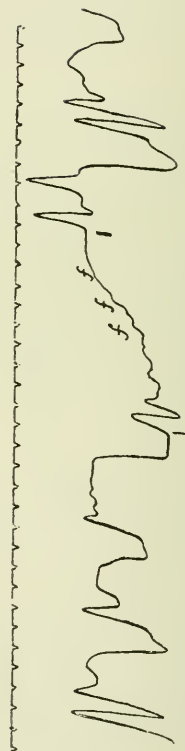


FIG. 4.

pulse was unaltered. The venous pulsation was less and the pain seemed relieved. A bran mash was eaten with some show of hunger. On the 30th the temperature fell to 102° and the pulse and respiration seemed improved; little or no jugular pulsation was evident. Hay and mashes were taken. The heart's action is said to have been normal on this day. On the 31st the temperature rose again, but no other symptoms reappeared. From this time until the night of January the 2nd the condition was unchanged. On that night a relapse occurred, the animal refused food and water and again showed evidence of pain. There is no note of the pulse condition at this time. On the morning of the 3rd, death occurred unexpectedly. The horse was found down in its stall with the neck bent under the body. He apparently fell suddenly and with great force against the iron manger, fracturing the cranium.

At the post-mortem the skull was found fractured. The heart appeared to be abnormal. It was unhealthy in colour, its walls were hypertrophied, a few white spots were visible on the endocardium, whilst the pericardium was also thickened and slightly dropsical. The valves were unaltered. The unexpected death of the horse precluded my seeing it.

Horse 3. The observations upon this mare were made through the kindness of Sir J. Macfadyean and Professor Woodruff.

It was a cart horse, aged 15 years, $16\frac{1}{2}$ hands in height. The past history was unknown. It was taken to the Veterinary College on account of breathlessness and staggering occasioned for some months by exertion.

I saw this horse on a number of occasions in January, 1910. The pulse was feeble and continuously and completely irregular; the rate was from 40-160 per minute. The heart sounds were clear; there were no murmurs. Little or no venous pulsation was visible in the neck while the animal stood in its stall, but it became prominent, and the rate of the heart beat increased, when it trotted a few hundred yards. The exertion also produced conspicuous dyspnoea.

Upon February the 12th, 1910, the horse was transported to some stables in the neighbourhood of University College Hospital Medical School and the stall was connected to the galvanometer. Curves were obtained by wrapping large pieces of cotton wool, soaked in saline, around metal electrodes and fastening these to the limbs or chest wall. The lead first adopted was from the right axilla to the left groin; curves were obtained which are exemplified in the third strip of Fig. 5. The curve may be compared with that taken from a horse by Einthoven (and published as Fig. 203 in Ellenberger and Scheunert's "*Lehrbuch der vergleichenden Physiologie der Haussäugetiere*," Berlin, 1910). Take first the ventricular complexes marked *R*, *S* and *T*; these portions of the curves are almost precisely the same as the corresponding phases shown in Einthoven's curve of the normal horse. They are sufficient to show that the ventricular beats in the abnormal curve are all of supraventricular origin. In Einthoven's curve each

ventricular contraction is preceded by an auricular representative, *P*, which is as prominent as the *T* shown in this strip. All trace of such variation is absent in the present instance, clearly pointing to an absence of co-ordinate and presystolic contraction of the auricle. The beats of Fig. 5 (strip *III*) are irregularly spaced; they lie at distances of 2.7, 2.9, 3.7 and 4.7 fifths of a second apart. The irregularity is of the characteristic form exhibited by a fibrillating auricle. The first two strips have a larger excursion. They were taken by applying the right forelimb electrode to the epigastrium, the left hindlimb electrode to the breast beneath the root of the neck. Compared with the third strip they are consequently inverted. These curves show the same summits *R*, *S* and *T*, but again no signs of co-ordinate auricular contraction. The rate is very variable. The irregularity in spacing is extreme. The heights of the opening variations of systole (notably *S*) are not proportionate to the pauses which precede the corresponding beats. These features are one and all characteristic of experimental fibrillation and complete irregularity of the human heart. There remains but a single feature and that is the oscillation, which is so typical in many experimental and clinical instances and which is due to the fibrillating auricle. It is obscurely seen in several places in these curves (and is marked *f*, *f*).

The pauses from beat to beat in a succession of 8 strips are tabulated and are given in the accompanying table. The successive beats read in columns from above downwards.

PULSE BEATS IN ONE-FIFTH SECONDS IN 8 STRIPS.
AS CALCULATED FROM ELECTRIC CURVES.

3.1	4.1	3.3	2.6	2.2	4.0	3.5	3.0
3.3	3.4	3.4	4.8	2.0	2.4	3.3	3.0
3.2	4.6	4.0	2.8	1.8	4.9	2.5	3.2
3.3	2.7	2.7	2.9	1.7	3.4	3.0	3.7
2.3	4.8	2.8	2.7	1.7	3.1	3.6	2.6
3.8	3.1	3.7	4.0	2.1	3.8	3.4	2.5
3.4	3.2	4.6		2.0	2.7	2.7	3.7
2.1	3.0			2.7	4.5	2.9	4.9
2.0	2.4			2.2	3.1	3.1	3.5
3.2				1.8	2.5	3.0	4.0
3.4				1.7	2.3	3.9	5.6
4.8				1.9	2.2	2.6	4.3
5.3				1.7	3.6	3.0	4.6
2.7				2.1	4.1	3.5	3.6
				2.4	3.1	3.5	2.7
				2.3	2.5	4.7	4.6
				2.6	2.4	5.4	4.5
				2.0	3.1	4.7	3.1
				1.6	3.2	3.6	
				1.7	3.8	5.7	
				3.6	2.6	3.2	
				2.0	2.3	2.4	
				1.7	2.0	4.3	
					3.6	3.0	
					2.7	2.9	
					4.2	3.7	
					3.6	3.6	
						3.9	
						3.2	
						4.0	

On February the 19th the horse was killed by a shot in the head, the trachea was immediately opened and artificial respiration was established. The chest was opened through an incision in the right chest wall by sawing through a rib. Unhappily, during the removal of the rib, the ventricle was damaged and considerable hæmorrhage occurred. There was, nevertheless, sufficient time for certain observations. The ventricle beat rapidly and irregularly, while the auricle seemed to be standing still. On catching hold of the ventricle and moving it, so as to obtain a closer view of the auricle, the former passed into fibrillation. A closer inspection of the right auricle now revealed the presence of a fine fibrillary movement in its walls. The movement was watched for some minutes, in fact till no visible contractions could be made out in either ventricle or auricle.

As a result of these observations I am able to state that in a horse which presented the characteristic irregularity, the ventricular beat was co-ordinate and of supraventricular origin, and further that the co-ordinate contraction in the auricle was in abeyance. I am unable to state that while the ventricle was beating co-ordinately the auricle was seen to be in fibrillation. But it was not contracting co-ordinately while the ventricle was beating in this fashion and it was seen to be fibrillating within a few seconds of the onset of ventricular fibrillation. We know quite definitely that fibrillation is not transmitted from ventricle to auricle, and we therefore have strong presumptive evidence that the auricle was fibrillating throughout. That the mechanism of the heart was not altered by the cerebral death of the horse is clearly shown by the continued irregular ventricular action. There is but a single source of error; it is possible that the same application of the hand and movement which induced fibrillation in the ventricle also induced fibrillation in the auricle, which was previously paralysed. But such an occurrence is in the highest degree improbable.

The heart was preserved. Its weight was 5,440 grammes.* It was sent to Dr. Cohn of New York. There was some dropsy of the subcutaneous tissues; the arteries and other organs seemed normal.

Horse 4. An old gelding of about 15 hands, the exact age and history of which was uncertain, was brought to University College Medical School from the Veterinary College on February the 18th, 1910. It was examined in the street. The animal was in a distressed condition. Dyspnœa was marked, there was some dropsy of the legs and abdominal parietes. It presented violent pulsation of the whole neck, which reached as high as the ears. It was obviously venous, and, so far as could be ascertained, systolic in time. The pulsation and the heart's sounds were extremely rapid, averaging 150 beats per minute; the several beats followed each other in the most confused and irregular manner. There were no murmurs.

* The heart weight for medium sized horses is given at 3 to 3.5 kilo. by veterinary text books.

Further observations were not possible ; and I was unable to purchase the animal or make any further investigation of it.

Horse 5. This horse was a gelding, aged 16, in height $15\frac{1}{2}$ hands. It was seen through the kindness of General Smith and Colonel L. Blenkinsop of Salisbury.

The symptoms had been present for 7 months. It had been under observation for 7 years, and was not known to have suffered from strangles or any other illness. The symptomatology consisted of very irregular and tumultuous action of the heart, marked breathlessness, epistaxis, faltering and occasionally falling, upon moderate exertion.

The horse was examined on Bulford Plain on June the 25th, 1910. The heart was absolutely irregular, long pauses of 2 seconds were frequent and short runs of rapid beats were noted from time to time. The rate was from 40 to 60 beats per minute, while resting. Upon exertion the rate showed increase, and a welling pulsation, not marked but distinct, appeared at the root of the neck. Breathlessness was fairly conspicuous after the animal had cantered a few times round a small paddock. The heart sounds were clear, there were no murmurs. The heart beats were more numerous than the arterial pulsations.

The horse was thrown in a covered yard and was chloroformed. It was then shot in the head, in compliance with the regulations, and the windpipe was opened. A good deal of blood poured from the trachea ; the shot had broken the base of the skull. As a consequence, artificial respiration was not free. The chest was opened by an incision on the right side and the removal of two ribs, and an excellent view of the beating heart was obtained. The ventricular movements were forcible and the spacing of the beats corresponded with what had been heard at the previous examination. For the horse they were rapid, and the irregularity was extreme. The ventricle showed no distension. At first no intrinsic movements could be seen in the auricle, it appeared to lie still except for the tugging transmitted from the ventricle. There was certainly no general shortening of its fibres. Closer inspection of the musculature revealed the presence of fibrillary movements. The epicardium covering the right auricle in the horse is comparatively thick and opaque and fibrillary movements are not readily seen in the underlying muscle. Close inspection of the ridges and, more especially, attention to the light reflections on its surface, particularly in the neighbourhood of the appendix, were conclusive. The independent movements of the several light reflections and the activity of the tissues generally was well displayed and was demonstrated to and recognised by the bystanders, including Colonel Blenkinsop. They were watched for several minutes, the ventricle continuing its active co-ordinate but irregular movements during the whole of this time. A hand was then placed under the ventricle, which was commencing to dilate, and in lifting it out of the pericardium it fibrillated. The auricle continued to fibrillate as before ; the two chambers were watched until all movements ceased in them.

The heart was removed, preserved and sent with the other specimens to Dr. Cohn. It weighed 4,335 grammes. The muscle was dark and friable. The pericardium and arteries seemed normal. The other organs presented little or no change.

Horse 6. While at Bulford Camp, I was shown another horse, stalled in the sick lines, by Colonel Blenkinsop. It was an old horse, suffering from chronic arthritic trouble. The heart beat at a normal rate, at or about 37 per minute. The beats followed each other perfectly regularly for about 10 or 15 cycles; a premature beat was then audible and it was followed after a prolonged pause by a further sequence of quite regular beats at the previous rate.

The irregularity obviously belongs to a distinct category; it corresponds to the single interruptions of a regular rhythm by pathological impulses in the human subject.

DISCUSSION.

The foregoing observations are sufficient to establish several facts. The horse suffers on rare occasions from irregularity of the heart's action, and the irregularity may be due to the presence of isolated premature contractions (*Horse 6*), or to a high grade of disorder in which the irregularity is complete. The completeness of the last irregularity has been observed in four separate animals and in two of these (*Horses 1 and 5*) graphic records have been obtained, confirming the subjective findings. The heart rate is variable but is generally increased. In the normal horse the rate lies between 35 and 40 per minute. When the gross irregularity is present the rate of the pulse may be decreased, presumably as a result of dropped beats; the heart rate on the other hand may accelerate to rates of 160 per minute for brief or long periods. The electrocardiograms (*Horse 3*) show that the irregularly beating ventricle is governed by impulses which descend to it through the auriculo-ventricular bundle and its branches; in every other way they correspond to the curves obtained in complete heart irregularity as it is observed in the human subject, and to the curves of auricular fibrillation as observed in experiment.

In two animals, from one of which graphic records were obtained, an inspection of the heart, beating *in situ*, revealed, first an irregularly beating ventricle and secondly a pulsationless auricle. In both, fibrillation of the auricle was witnessed. In the first of these observations (*Horse 3*) damage was done to the ventricle in opening the chest and there may be some doubt as to whether the auricular fibrillation did not follow upon this damage. This doubt is removed, for a precisely similar phenomenon was seen in the second observation (*Horse 5*), and in this instance no such damage occurred. The heart, at the inspection of it, was beating actively and was in good condition.

The presence of the same form of mechanism before and after the cerebral death of the animals and the resection of the ribs can scarcely be doubted, for the ventricular action remained constant throughout the whole of the preliminary procedures in both instances.

We are left with the conclusion that chronic fibrillation of the auricle is a pathological fact in horses, and that it is associated with an action of the heart which is in every way similar to that known as complete irregularity of the heart in man and to the irregularity which supervenes when the auricles are forced into fibrillation in the dog or cat.

Taking this evidence and that which has been previously recorded into consideration, the final conclusion that the three ventricular irregularities, namely, that which is found in the horse, that which is observed in man and that which is induced in the dog or cat, are one and the same seems indisputable. They are all dependent upon one underlying factor, namely inco-ordinate or fibrillary contraction of the auricular tissues.

It is of interest to observe that in none of the five instances of auricular fibrillation in the horse was there any definite evidence of valvular lesion. It is known that in many of the human patients the valve segments are intact. The underlying mischief must be sought in the musculature itself. It is with this in mind and with a view to the eventual comparison of the human and equine material that I have asked my friend Dr. Cohn, whose knowledge of these muscle changes is so full, to undertake a detailed examination of the hearts which I have been able to obtain.*

CONCLUSIONS.

1. Horses are on rare occasions the subjects of two forms of irregularity of the heart. One of these consists of isolated premature contractions. The other is a complete irregularity.

2. The complete irregularity which occurs in the action of the ventricle of horses may be seen, from inspection of the heart as it beats *in situ*, to be associated with fibrillation of the auricles; a condition which must therefore be held as a proved pathological condition in these animals.

3. Fibrillation of the auricles in horses gives rise to a condition in which the symptomatology, and especially the graphic records, are identical in all their classical features, with a condition known as complete irregularity of the heart in man.

4. Complete irregularity of the heart in man is unquestionably associated with fibrillation of the auricles.

5. Fibrillation of the auricles in horses is usually unaccompanied by valvular lesions. It is accompanied by grave circulatory troubles which may be classed under the general term of heart failure.

* Brief reports of these findings have been published in *Heart*, 1909-10, 1, 306, in the *Verhandl. d. deutsch. pathol. Gesellsch.*, 1910, 112; and in the *Mechanism of the Heart-beat*, London, 1911,

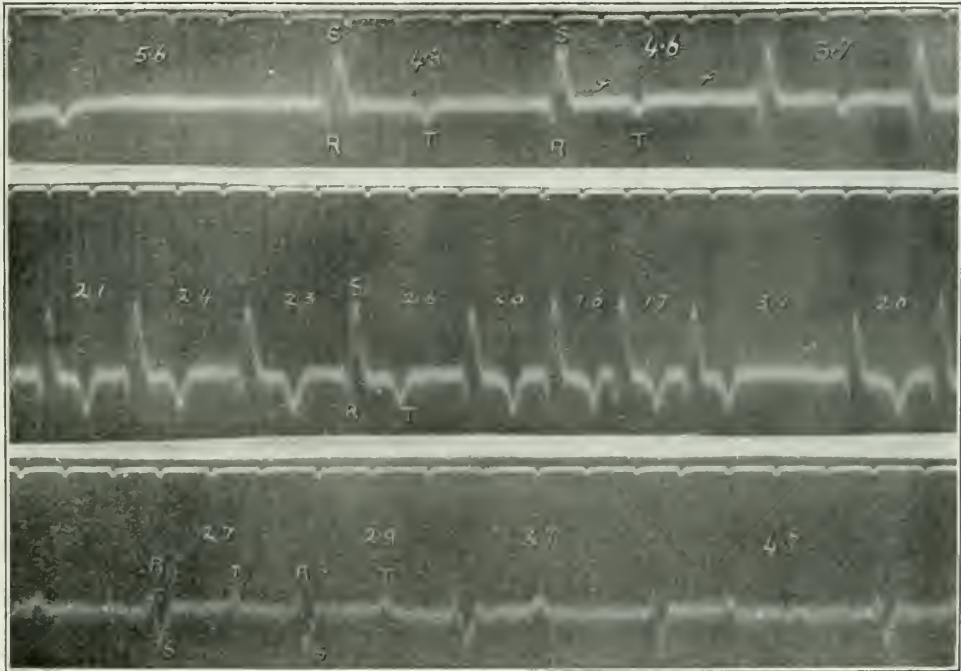


Fig. 5. ($\times \frac{3}{5}$). Three electrocardiograms from the third horse, the last strip is from the right fore-limb and left hind-limb. Complete irregularity of the heart is present, each heart cycle is represented by *R*, a large *S* and a *T* variation: there is no sign of *P*. There are traces of oscillations in the longest diastolic periods shown.

The first two strips were taken from the epigastrium and centre of the breast in front: (they are consequently inverted). They show the same characters as those exhibited by the third strip. The irregularity is of high grade, the heart rate at times exceeds 150 per minute (normal 35-40). Oscillations are most distinct in the first strip. *P* is completely absent.

THE RELATION OF REGULAR TACHYCARDIAS OF AURICULAR ORIGIN TO AURICULAR FIBRILLATION.

By THOMAS LEWIS* AND H. G. SCHLEITER.

(From the Cardiographic Department, University College Hospital Medical School).

IN the present communication we wish to record two cases of paroxysmal tachycardia which present features of exceptional interest. We utilize these two cases to illustrate the main thesis of this paper, namely, the close pathogenetic relation of regular tachycardia arising from an abnormal auricular focus and auricular fibrillation. The cases are of importance in that they support the general hypothesis that auricular fibrillation consists of an exaggeration of the phenomenon of pathological or heterogenetic impulse formation, which accounts for a large group of simple tachycardias arising in the auricle.

CASE 1. Paroxysms of auricular fibrillation. On one occasion a recorded paroxysm started as fibrillation and terminated as a regular tachycardia, springing from an ectopic auricular focus.

A. J., a cabinet maker of 28 years, was first seen on November the 11th, 1910, at the out-patient department at the City of London Hospital, in an attack of paroxysmal tachycardia. He has been under observation since that date and a number of paroxysms have been observed.

History. His mother died of "heart disease" 4 years ago; she is said to have had rheumatic fever. A letter from Dr. Hargrave, who attended her in her last illness, tells us that she succumbed to progressive failure of the heart, which resulted from asthma and chronic bronchitis. His brothers and sisters, of whom four are alive, have never suffered from tonsillitis, rheumatism, chorea or heart disease. His two children are alive and healthy. One sister died of enteric.

Personally he has had no previous illness, excepting measles as a child and an occasional cold. Rheumatic affections and syphilis are denied. He has always been moderate in the consumption of alcohol and tobacco.

Two years ago he had his first heart attack, and since that time has been subject to them at intervals of 1-3 months. He attributes the first attack to strain, as it came on while he was lifting a heavy piece of furniture. The attacks usually last 15-18 hours. Lately they have been more frequent and some have lasted longer. The shortest attack has been 7 hours, the longest 3½ days. He states that the attacks come on at any time; they have often commenced in the night; exertion predisposes to them. They are not influenced by diet, so far as he knows. They commence quite abruptly and end in the same fashion; the cessation is always marked by considerable relief.

The first symptoms of the attack are faintness and sweating; a few minutes later he is conscious of palpitation, and feels cold and sick. Vomiting is said to occur ½-1 hour later, and about the same time he is aware of a fixed pain in the front and lower part of the chest. A

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little later, the pain increases and is more prominent at the pit of the stomach and over the right ribs. It also radiates to the shoulders. He becomes very exhausted, thirsty and short of breath. Flatulence is a prominent symptom of the attacks and may precede them.

Between the attacks he is fairly well. He can walk in comfort, but easily gets giddy. If he is sitting and rises suddenly, the giddiness may cause unsteadiness and he supports himself, fearing a fall. He sometimes gets a little breathless after walking up one short flight of stairs. The appetite is good and he sleeps well; the bowels are opened regularly. He suffers from wind, and has had vomiting during the past few months. On several occasions, bright blood has been brought up.

During the last six months, he has done no work. He has lost ten pounds in weight in the past two years.

Observations between the attacks.—The patient is well built and nourished. He has a healthy, in fact somewhat excessive, colour. There is no trace of cyanosis. The lungs are normal; the nervous and alimentary systems present no objective signs of disease. The urine is normal.

The liver dulness extends from the upper border of the 6th rib to the costal margin, its edge is not palpable. The spleen is not felt. The thyroid and lymphatic glands are normal. The limits of cardiac dulness are normal, lying 0 and $3\frac{1}{2}$ inches to right and left of the mid-sternal line. At the apex there is a short systolic thrill and a harsh systolic murmur. Otherwise the heart sounds are normal. The arteries are somewhat thickened; the systolic blood pressure varies between 70 and 120 mm.Hg., (Riva Rocci). The heart beats regularly as a rule (Fig. 1 and 8). Its rate lies between 50 and 78 per minute. At times, sinus irregularity has been present. The *a-c* interval is usually one-fifth of a second in length (Fig. 1). During the stays in hospitals, his temperature has always been normal.

Observations during the attacks.—On three occasions, he has been admitted to the City of London Hospital in attacks (November the 9th, 1910, December the 8th, 1910, and August the 4th, 1911); he stayed at Mount Vernon Hospital from February the 2nd till March the 11th, 1911, and on two occasions he has been taken in at University College Hospital for attacks (May the 31st and July the 1st, 1911). During his last stay at University College he developed an additional attack. On no other occasion has a paroxysm commenced during his hospital stays, most of which have been of several weeks or months duration.

The attacks which have been observed have all been of over 12 hours duration and on one occasion a paroxysm lasted $3\frac{1}{2}$ days.

Seen within half an hour of the onset he is already distressed. The face is pale and sunken; he is restless and complains of distress of breathing and precordial pain. As the attack progresses his symptoms become aggravated, some cyanosis appears, the respirations increase in rate and the pallor becomes more conspicuous. The heart dilates and the liver becomes swollen and pulsates. Dropsy has not been noticed, and there have been no physical signs of œdema of the lungs. He is salivated during the attacks, develops a cough and when they have lasted many hours commences to expectorate a little frothy mucus.

The swelling of the heart may be exemplified by the following observations. When originally seen during a paroxysm in November, 1910, the measurements on percussion were $\frac{1}{2}$ and $5\frac{1}{2}$ inches respectively. At the end of a long paroxysm of 24 hours duration, on May the 31st, 1911, they were 2 and $5\frac{1}{2}$ inches. 5 hours after the cessation of the same paroxysm they were $\frac{3}{4}$ and $3\frac{1}{2}$. On July the 1st, they were 2 and $6\frac{1}{2}$ inches, 2 hours after the onset. 7 hours subsequent to the offset of the attack they were 0 and 4. 15 minutes after the onset of the attack of July the 15th, they were 0 and $5\frac{1}{2}$, the patient lying quietly in bed; a few minutes' restiveness was accompanied by a decided increase in the dull area. A definite and striking change to $\frac{3}{4}$ and $6\frac{1}{2}$ inches was observed and it persisted. 1 hour later, the paroxysm continuing, the measurements were recorded at $1\frac{1}{2}$ and $6\frac{1}{2}$. Next morning the paroxysm had ended and the limits were 0 and $4\frac{1}{4}$.

The nature of the paroxysms.—The majority of the paroxysms have consisted of attacks of auricular fibrillation, during which the heart rate has varied between 155 and 200 per minute. At such times the venous pulse has been of the ventricular form. Paroxysms of this nature have been observed and recorded on five occasions; examples of the curves are shown in Fig. 3, 4 and 10.

The second form of paroxysm, which was recorded electrocardiographically on one occasion only, consisted of a regular tachycardia, the average rate of which was 140 per minute. It arose from an ectopic focus in the auricle and formed the termination of a long paroxysm which commenced as fibrillation (Fig. 2 and 9).

The graphic records of observed attacks are summarised in the following table.

1st paroxysm.	9/xi/1910.	Auricular fibrillation (lasting many hours). (Venous curves).
2nd paroxysm.	8/xii/1910.	Regular paroxysm. (Lasting approximately 12 hours). (Venous curves taken but mislaid).
3rd paroxysm.	25/ii/1911.	Auricular fibrillation. (Lasting 10 hours).
4th paroxysm.	31/v/1911.	Auricular fibrillation. (Lasting 12 hours). (Electrocardiograms, 3 leads).
5th paroxysm.	1/vii/1911.	Auricular fibrillation. (Lasting $3\frac{1}{2}$ days). (Electrocardiograms, 3 leads, Fig. 10.)
	2/vii/1911.	Tachycardia of auricular origin. (Electrocardiograms, 3 leads, Fig. 9 and venous curve, Fig. 2).
6th paroxysm.	15/vii/1911.	Auricular fibrillation. (Lasting about 10 hours). (Polygraphic curves and electrocardiograms, 3 leads).
7th paroxysm.	4/viii/1911.	Auricular fibrillation. (Lasting approximately 24 hours). (Polygraphic curves)
Control curves of the normal rhythm were taken on a number of occasions, (1/vi/1911, 4/vii/1911, 14/vii/1911, 19/vii/1911, 21/vii/1911, 24/vii/1911, etc.).		

The polygraphic curves are exemplified by Fig. 1-4. The curves are not treated chronologically. Fig. 1 shows venous and radial curves, taken on July the 21st, 1911, during a period when the pulse was slow (63 per minute) and regular. The *a-c* interval is one-fifth of a second.

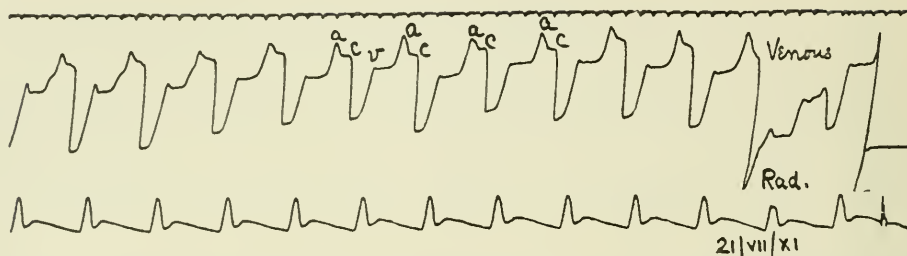


Fig. 1. *CASE 1.* A polygraphic curve taken while the heart's action was slow and regular. The *a-c* interval is $1/5$ sec.. The pulse rate is 63 per minute. (July the 21st, 1911). The time-marker of all the polygraphic curves is in $1/5$ sec..

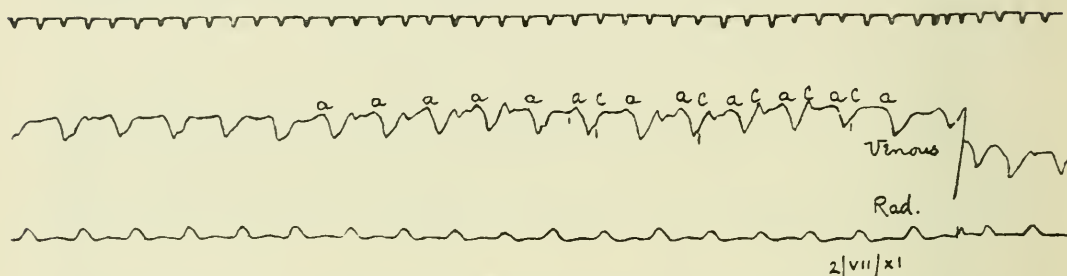


Fig. 2. *CASE 1.* A polygraphic curve taken during the long paroxysm observed on July the 2nd, 1911. The heart's action is regular; the rate is 142 per minute; the *a-c* interval is a full $1/5$ sec..

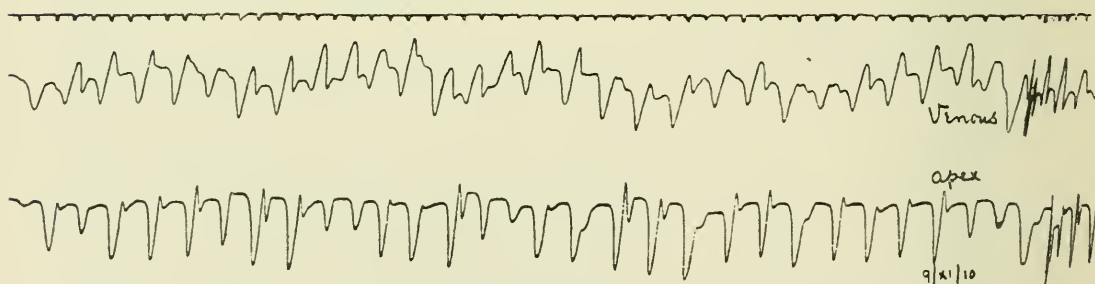


Fig. 3. *CASE 1.* A jugular and apex curve, taken during a paroxysm of tachycardia, (November the 9th, 1910). The heart's action is irregular; the rate is 165 per minute. The jugular pulse is of the ventricular form.

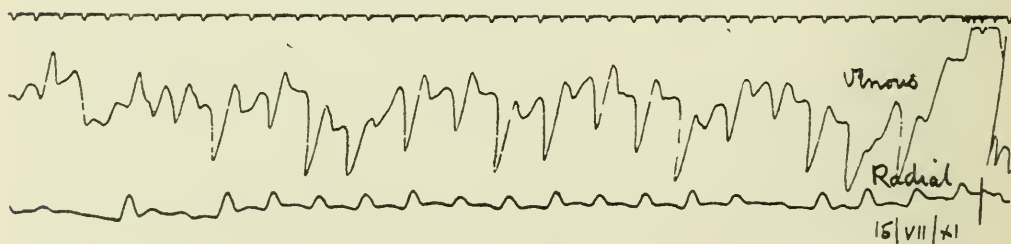


Fig. 4. *CASE 1.* A jugular and radial curve taken during a paroxysm of tachycardia, (July the 15th, 1911). The heart's action is irregular; the rate is 155 per minute. The jugular pulse is of the ventricular form.

Fig. 2 shows venous and radial curves taken at the end of a paroxysm on July the 2nd, 1911. The heart's action is regular; its rate is 142 per minute. The *a* wave is small and obscure. The *a-c* interval is one-fifth of a second. A number of observations were made upon the effect of certain events upon the rate of this paroxysm. Repeated swallowing had no influence on the rate. Changing from the sitting to the lying posture did not influence the heart's rate by more than two beats per minute. Repeated suspension of respiration had little or no influence upon the rate.

Fig. 3 and 4 are examples of curves taken during paroxysms on November the 9th, 1910 and July the 15th, 1911, respectively. Fig. 3 shows a venous and apical curve, Fig. 4 shows a venous and radial curve; in both, the heart is beating irregularly and the venous curve is of the ventricular form.

Electrocardiograms of the three separate mechanisms are shown in Fig. 8, 9 and 10. Each figure includes a series of three leads, marked *I*, *II* and *III* respectively. These represent Einthoven's usual leads in each instance: *I*, right arm to left arm; *II*, right arm to left leg; *III*, left arm to left leg. In each series the second lead is standardized so that 1/1,000 volt equals 0.6 cm. in the reduced curve.

The curves are not treated in chronological order. They are simply given as examples of the mechanisms which have been observed.

The normal mechanism has been recorded electrocardiographically on two occasions, on June the 1st, 1911 and on July 4th, 1911. The curves are identical for the two dates. Speaking of Fig. 8, each cardiac cycle of the regular mechanism shows auricular (*P*) and ventricular (*R*, *S* and *T*) representatives. *P* is prominent and bifurcates at its summit in leads *I* and *III*. The *P-R* interval is 0.14 sec.. The rate of the heart beat is 65 per minute.

This series should be compared with the two following series, Fig. 9 and 10. Fig. 9 was taken during the regular paroxysm of July the 2nd, 1911. Lead *I* shows *R* and *T* summits. *T* is inverted. (The first lead of the normal mechanism, Fig. 8, shows no *T* summit). *P* is very indistinct in this lead. In the second lead *R* and *T* waves are well represented; *R* is of less amplitude than in the normal mechanism. In Fig. 9 *II*, *P* is clearly represented as a complex curve, consisting of downward, upward and downward deviations. The third lead shows a diminished *R*, an increased *S* and an upright *T*. *P* is very similar to that found in lead *II*. The rate of heart-beat in this figure is 140 per minute. The *P-R* interval is approximately 0.18 sec. in duration. Comparing the two series of curves, it is seen that the ventricular complexes of the tachycardia and normal rhythm, Fig. 8 and 9, correspond fairly closely in the respective leads; the variations are chiefly in the amplitude of the various summits, and in an occasional inversion of *T*. The resemblance is sufficiently close to allow us to conclude that the origin of the heart beat is supraventricular during the tachycardia. The auricular origin of the paroxysm is proved by the presence of the clear auricular representatives in leads *II* and *III*. Nevertheless, the paroxysm

has originated in a focus at some distance from the natural pace-maker, as is indicated by the anomalous appearance of these auricular representatives. At the time when the electrocardiograms of the regular paroxysms were obtained, the movements of the string were watched and occasional premature contractions, interrupting the paroxysm itself, were observed, but were not recorded. The ventricular portion of such cycles seemed to give exactly similar electric complexes to those of the remaining paroxysmal cycles. The premature contractions, therefore, were presumably of auricular origin also.

The third mechanism is shown in Fig. 10, curves taken on July the 1st, 1911. They are from the beginning of the paroxysm of which Fig. 9 shows the termination. Similar curves were obtained on May the 31st, 1911, and on July the 15th, 1911. The ventricular complexes in Fig. 10 are similar in the three leads to those of the corresponding leads in Fig. 9. The beats are placed at quite irregular intervals throughout the curves. The rate is variable, but at times it reaches nearly 200 per minute. *P* summits are entirely absent in all the curves. No two adjacent cycles are exactly alike. The slight variation from cycle to cycle is due to the presence of the characteristic oscillations of auricular fibrillation, which are most conspicuous where the diastoles are relatively long, (*f.f.*)

CASE 2. Short and long paroxysms of tachycardia; the majority of the paroxysms were short and consisted of regular tachycardias springing from an abnormal focus in the auricle. They were occasionally interrupted by beats from a second abnormal auricular focus. On one occasion, curves showing the passage from the regular mechanism to auricular fibrillation were obtained.

G. T., a married man, aged 71, came to the City of London Hospital on May the 28th, 1911, complaining of chronic cough, pain in the chest and lower part of the back, together with occasional stiffness in the right upper limb.

History. The father and mother died at the ages of 81 and 77 respectively. Five brothers are dead, one, it is said, of heart disease; one sister is alive and in good health. He has had twelve children, four of whom died in infancy; of the remaining eight, one is tuberculous and the others are healthy. The wife, aged 52, has had one miscarriage. The patient, formerly a wood carver, is now an old age pensioner. In infancy he had measles and whooping cough. At the age of 51, he was in the Bethnal Green Infirmary for pleurisy and inflammation of the lungs. A few years later he had rheumatic fever. He states that he was laid up three years ago with a second attack of pneumonia. On the whole he affirms that he has enjoyed fair health. He denies venereal infection. In his younger days he drank ale freely. As a smoker, he has been moderate.

His present illness dates from 1908, when he first experienced cough and pain in the chest and lower part of the back. For the most part, pain has been referred to the precordium. It is gnawing in character and is related to meals. Sometimes it is said to have been so severe as to make breathing difficult, a feature which suggests for it a cardiac origin. Shortness of breath and palpitation of the heart have been noticed upon exertion. He has suffered from, and still has, a chronic cough with a slight expectoration of mucus. There has been no hæmoptysis. His appetite is poor, he sleeps badly and gets up at night to pass water.

Observations between the attacks of tachycardia.—The patient is an undersized and poorly nourished individual. His skin is sallow. There is no œdema or cyanosis. The veins of the lower limbs are varicose. There is extensive pyorrhœa. The thyroid is not enlarged. There is evidence of a mild degree of emphysema. There are fine crepitations at both bases. The nervous and alimentary systems present no signs of importance.

The heart's apex beat is in the 5th interspace, $4\frac{3}{4}$ inches to the left of the middle line. There is systolic retraction in the 5th interspace internal to the apex. The limits of the heart's dulness lie 0 and $4\frac{3}{4}$ inches to the right and left of the mid-sternal line, respectively; they do not change with posture. The heart's sounds at the apex are clear and show no alterations. There is a musical systolic murmur after the first sound, and it is transmitted to the left axilla. The aortic second sound is somewhat increased in intensity. A regular heart rhythm is interrupted by premature beats, which are fairly frequent; most of them reach the wrist. The arteries are thickened but not tortuous. The pulse is of good volume. The systolic blood pressure is 120 mm. Hg..

The upper level of liver dulness commences at the 7th rib; the lower limit is at the rib margin. Neither liver nor spleen is to be felt. There is no abdominal tenderness or other abnormality. The urine is normal. A Wassermann reaction is negative.

Observations upon the paroxysms.—Short paroxysms of tachycardia have been recorded upon almost all of the numerous occasions of examination. Nevertheless they are relatively infrequent; as a rule two or three paroxysms occur during the two or three hours of investigation. They last for a time varying from two or more seconds to an hour. The majority of the paroxysms last from 10 to 20 seconds. The patient is absolutely unconscious of onset and offset and is unaware of the paroxysm while it is present. Apart from posture, we have been unable to ascertain that any factor influences the presence or absence of paroxysms to any real extent; they appear to be more frequent in the standing and sitting postures.

With a solitary exception, an exception which will be described in detail, the recorded paroxysms have consisted of regular tachycardias, the rate rising from the normal of 80 or 90 beats per minute to 122 or 170 per minute. The usual paroxysmal rate is between 135 and 145 per minute. These paroxysms are due to new rhythms arising from an abnormal point in the auricle. On one occasion, after a prolonged period of regular tachycardia, the mechanism altered to fibrillation. The preceding regular tachycardia was the most rapid observed, namely 170 beats per minute. The rate during the fibrillation was variable, it rose at times to 190 beats per minute.

Description of the graphic records.—Examples of paroxysms as they appear in radial pulse curves are shown in Fig. 5 and 6. Fig. 6 shows a

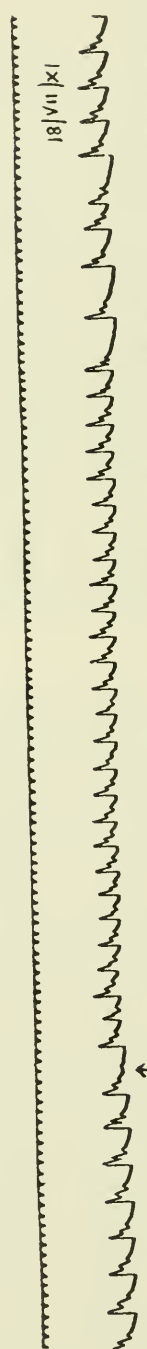


Fig. 5. *CASE 2.* A paroxysm of regular tachycardia taken on July the 18th, 1911. It lasts 14 seconds. The first beat of the paroxysm fails to affect the pulse. The paroxysm is followed by a long post-paroxysmal pause and a period of retarded pulse rate, which is interrupted by a single premature beat. The time-marker in all sphygmographic curves is in 1/5 sec.,

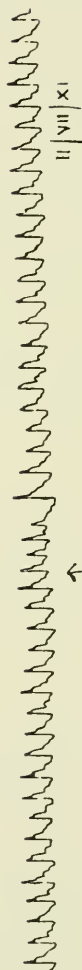


Fig. 6. *CASE 2.* A short paroxysm of 4 beats taken on July the 11th, 1911. The paroxysm starts abruptly and finishes equally suddenly. It is followed by a post-paroxysmal pause and by a short period of pulse retardation.

paroxysm of 4 beats only. Fig. 5 is an example of a paroxysm of longer duration. Most of the paroxysms have been similar to that portrayed in this curve. The onset and offset are quite abrupt. The offset is marked by a considerable degree of pulse slowing which vanishes within a few cycles; this phenomenon has been observed in many previous cases. A single premature contraction interrupts the normal rhythm shortly after it is resumed (in Fig. 5).

The premature contractions which interrupt the slow rhythm are of four kinds. Very occasionally the points of origin lie in the ventricle. The electrocardiograms have shown that some of these premature ventricular beats arise in the left or apical portions of the ventricle, some in the right or basal portions of the ventricle; we do not consider it necessary to reproduce the figures. The majority of the premature beats have arisen in the auricle; and they originate in two auricular foci, both of which lie at a distance from the pacemaker. The two types are illustrated by Fig. 12 and 15. In Fig. 12 the normal rhythm, to which the first three and the last cycle belong, is interrupted by a single premature contraction, arising in the auricle and represented by *P*, *R* and *T* summits. The *R* and *T* summits of the premature beats are similar to those of the rhythmic beats. The *P* summit of the premature beat is partly iso-electric, but is mainly a deviation in the upward direction; it differs from the *P* summits of the rhythmic beats. The second type of premature auricular contraction is shown in Fig. 15. As in the first type, the ventricular complex is similar to that of the rhythmic beats. On the other hand, the auricular representative is of different form. It consists of a deviation in the downward direction.

The short and regular paroxysms, a very large number of which have been observed, have been of one type. They are illustrated by Fig. 13, 14 and 16. They consist of a succession of beats arising in the auricle at the same point from which the second type of single premature beat is shown to arise (Fig. 15). The centre of such a paroxysm is published in Fig. 13, in which the rate is approximately 140 per minute. The cycles consist of a downwardly directed auricular representative *P*, and the usual summits *R* and *T*, corresponding to the ventricle and of similar form to those of the rhythmic beats. The termination of a similar paroxysm is shown in Fig. 14. In a very large number of the observed paroxysms, single beats springing from the auricle, but arising in a focus which is distinct from that at which the usual paroxysmal beat originates and from that at which the rhythmic beat of the slow periods arises, interrupt the paroxysm itself. Two examples of this phenomenon are shown, namely, the last cycle but one in Fig. 13 and the last cycle of the paroxysm in Fig. 14. The majority of these interrupting beats are slightly premature in relationship to the rhythm of the paroxysm. This is shown in Fig. 14, but in Fig. 13, the interrupting beat falls at its proper time. A comparison of the interrupting beats with the premature beat of Fig. 12 shows that they arise from the same focus. It has been remarked that they frequently terminate a paroxysm.

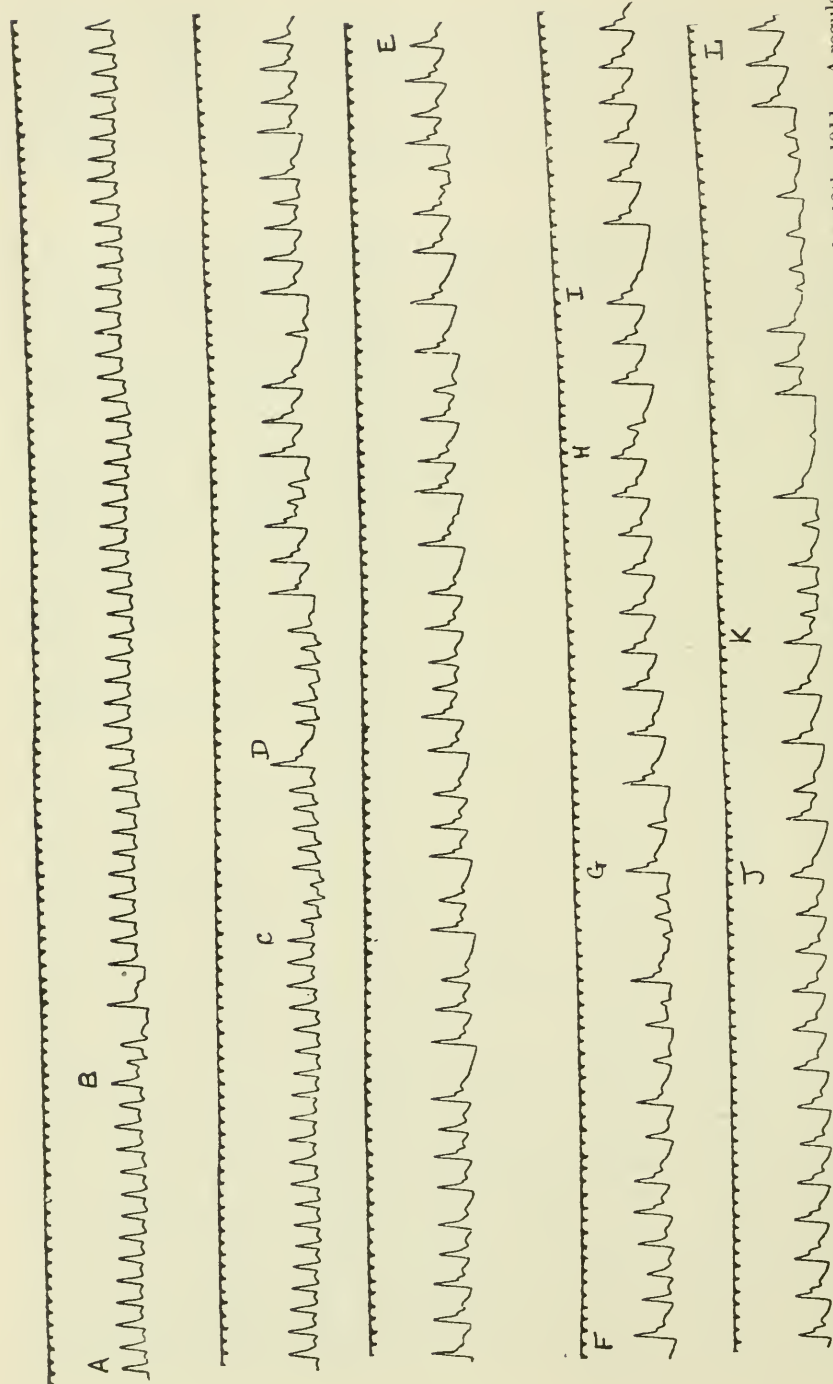


Fig. 7. CASE 2. Portions of a continuous sphygmographic curve taken from the radial artery on July the 18th, 1911. A regular paroxysm preceded it up to the point marked A; it is continued, with the exception of a short irregular period at B, up to C. At this point the pulse becomes irregular and at D the irregularity is complete. At D the auricle is fibrillating; the fibrillation is continued between D and E. Between E and F a portion of similar curve of 45 seconds duration has been excised. The fibrillation terminates at G, where the normal rhythm, interrupted by solitary premature beats, takes its place. Premature beats are seen at H, I and J. At K fibrillation sets in once more and the commencement of an attack of over one hour's duration is shown.

To sum up, the paroxysms consist of beats which arise in a single abnormal focus in the auricle and these abnormal or ectopic rhythms are disturbed by interruptions from a second ectopic focus. It is noteworthy that both the types of beat found during the paroxysms are also found as interruptions of the normal slow rhythm. Briefly, the patient possesses two foci of irritation in the auricle, each of which lies at a distance from the pacemaker. Both foci generate single new impulses and one of them generates impulses in succession.

We now pass to a description of certain events recorded on the 18th of July, 1911, and we may conveniently commence with a description of a continuous sphygmographic curve taken over a period of several hours on the afternoon of that day, (Fig. 7). When the patient first came under observation, the pulse was very irregular, but by the time the sphygmograph had been arranged, it was regular and beating at an approximate rate of 170 to 180 per minute. The patient exhibited a regular paroxysm of the usual form, though of somewhat faster rate. The regular paroxysm ran for 72 seconds, up to the point marked *A* in Fig. 7. At the point marked *B*, it became irregular for a second or more. The continuous curve is given in successive strips. At *C* the pulse shows some irregularity. At *D* it becomes very irregular and assumes the form which is so characteristic of auricular fibrillation. The same mechanism is continued from *D* to *E*; between *E* and *F* a portion of the curve of 45 seconds' duration and of precisely similar form has been excised. From *F* to *G* the fibrillation continues. At *G* the normal rhythm is resumed, but is interrupted by occasional premature beats at *H* and *I*. The normal rhythm is continued up to the point marked *J*. Occasional premature contractions then appear, and at *K* the complete irregularity, which is characteristic of a fibrillating auricle, commences again and continues to the end of the tracing (*L*). Following upon this strip, the completely irregular pulse continued for 69 minutes. The normal rhythm reappeared for 32 minutes. It was then interrupted by a paroxysm lasting 14 seconds. This paroxysm is shown in Fig. 5. A period of normal rhythm of 6 minutes' duration followed, and this in its turn was succeeded by a regular paroxysm of 21 seconds duration. The normal rhythm which followed was watched for 25 minutes, when the observations came to an end.

During the progress of the continuous radial curve, a large number of electrocardiograms were obtained. The first curve (Fig. 16) was taken somewhere between the points *A* and *D* in Fig. 7. The paroxysm consists of a succession of beats of a similar character to those shown in Fig. 9. The two curves differ mainly in rate. A second electrocardiogram (Fig. 17) was taken shortly after the onset of the complete irregularity (Fig. 7 *D*). Fig. 18 was taken during the stage of complete irregularity following *L* (Fig. 7).

The electrocardiograms, Fig. 17 and 18, testify conclusively to the presence of fibrillation of the auricles. The ventricular beats, represented by *R* and *T* summits of the usual form, are scattered throughout the curves

at irregular intervals. The summits *R* are separated by portions of curve which differ slightly from each other from cycle to cycle; this variation is due to the presence of the characteristic oscillations of auricular fibrillation, which are most marked in Fig. 18 (*f, f*).

In most instances of paroxysmal tachycardia arising in the auricle, whether the paroxysms originate in a single focus and are regular or whether the paroxysms originate in fibrillation and are irregular, it is noted that the height of the peak *R* during the paroxysmal stage is increased as compared with the normal. In the present case we have been unable definitely to ascertain the presence of this phenomenon, and probably this has been due in some measure to a phenomenon of an exceptional kind. In a number of radial curves obtained from the patient, very distinct evidence of a *pulsus alternans* has been obtained from time to time; and in electrocardiographic curves taken during the normal periods, a considerable variation in the amplitude of *R* has been frequently observed; this variation has not necessarily occurred in alternate fashion. This is well shown in Fig. 11, in which two *R* summits of large amplitude are followed by two *R* summits of lesser amplitude. Similar variations of amplitude have been frequently met with during the paroxysms. A notable example is shown in Fig. 13. A comparison of amplitudes during normal and paroxysmal periods has consequently been difficult or impossible.

DISCUSSION.

As we stated in our introductory remarks, the main object of this paper is to correlate two conditions, regular paroxysms of tachycardia arising in the auricle and auricular fibrillation. But while this is the main proposition before us, it is necessary to go somewhat further afield, and to collect certain accessory evidence bearing upon the production of pathological beats in the auricle. The view that tachycardia of auricular origin and auricular fibrillation have a common pathogenetic basis is but part of a more general conclusion. This general conclusion was dealt with by one of us at considerable length in a recent publication.¹⁰ The view is held in respect of both divisions of the heart, namely, auricle and ventricle; it is that there are three chief stages in the production of those pathological impulses which have been termed heterogenetic. There is the single and isolated heterogenetic impulse which gives rise to the simple premature contraction; there is the series of heterogenetic impulses giving rise to a new regular and fast rhythm; and, finally, there is the condition in which multiple foci are active and in which the musculature is so disturbed by impulses thrown out from multiple centres, that co-ordinate contraction is impossible and a state known as fibrillation ensues. The conception is that the three stages in the disorder of a division of the heart are due to a single underlying phenomenon, namely heterogenetic impulse formation. Variation in the degree of disorder is attributed to a variation in the degree of muscular

irritability in response to the exciting agent, or to a variation in the strength or distribution of the exciting agent. While the actual observations of this paper are more especially directed towards the proof of the close inter-relationship of new rhythms and fibrillation, it may be well to bring forward, in a general survey, the main facts upon which the general conclusion rests and to treat the special proposition of this communication as an integral part of it. The evidence is summed up in the following paragraphs.

1. When a weak faradic current is applied to the auricle or ventricle, and this current is gradually strengthened, a series of events is recorded. Single premature beats are first seen. An increase of current produces a regular tachycardia. Finally, with the strongest current, the muscle passes into fibrillation.

2. Many interferences with the muscle of the heart, as for example the administration of light percentages of chloroform or the injection of adrenalin⁴ or obstruction of the coronary vessels,⁶ awaken similar series of events. Single interruptions of the normal rhythm appear and these are succeeded by tachycardia and fibrillation, originating in the muscle affected.

3. A recent observation connects the tachycardias and fibrillation. It is well known that if an auricle be subjected to a fairly powerful faradic current and fibrillation is induced, it frequently happens that, at the cessation of stimulation, the fibrillation continues for some little while. The phenomenon is referred to by German writers by the apt term "*Nachflimmern*." We have observed the repeated replacement of this "*Nachflimmern*" by a regular tachycardia.

4. If a regular tachycardia is produced in the auricle by means of a weak faradic current, vagal stimulation will sometimes convert the tachycardia into auricular fibrillation.¹⁰

We may now sum up certain clinical evidence.

5. It is a usual experience in observations upon clinical cases of tachycardia of auricular or supraventricular* origin to find that the slow periods which separate the paroxysms are interrupted by premature beats of a precisely similar† nature. Our own observations include six cases, of which five have been previously recorded, ^{5, 7, 8 and 9} and the second case of the present communication forms the sixth. Similar observations have been made by Cohn¹ and Laslett.³

6. Curves showing intermediate or transitional conditions between single premature contractions and long paroxysms of tachycardia are not

* We insert the word supraventricular, because in some of the cases it has been impossible definitely to establish the auricular origin of the paroxysm, although their generation in this division of the heart is probable in most of the instances referred to.

† Precisely similar in so far as the graphic methods employed are concerned.

infrequent in given cases. An example is shown in Fig. 5, where four premature beats follow each other in succession. Other examples might be referred to (Lewis,⁹ Cohn¹ and Laslett's³ cases).

7. In patients who exhibit paroxysms of auricular fibrillation, the slow rhythm, which separates such paroxysms, is frequently interrupted by single premature auricular contractions. Two instances of this nature have come under the observation of one of us and have already been recorded.⁸ A series of similar cases was previously reported by Mackenzie.¹¹ An important instance of an allied type of case has been described by Hewlett,² a case in which certain transitions between the one form of irregularity and the other were observed.

8. Paroxysms of regular tachycardia of auricular or supraventricular origin and paroxysms of auricular fibrillation may occur in one and the same case. The writers have had an opportunity of studying a series of such cases and the two cases recorded in this paper are examples of this association. Moreover, the direct passage of regular paroxysms into fibrillation or fibrillation into regular paroxysms has been repeatedly observed. The original observation was made upon a case in which short paroxysms of regular tachycardia arising in the auricle interrupted the normal rhythm.⁸ On one occasion while electrocardiographic curves were being taken, the mechanism changed from tachycardia of auricular origin to auricular fibrillation, and subsequently the regular paroxysm was resumed. The same phenomenon probably occurred in Hewlett's case² (cp. Fig. 5 of his paper). It has also been recorded in a case described by Mackenzie¹² and in a case described by Turnbull;¹³ (in the latter the actual passage from one to the other was not caught). In the former the passage from one to the other was frequently caught. In the present paper, we have added two cases: in *CASE 1* a long paroxysm of many hours duration commenced as auricular fibrillation and terminated as a tachycardia of auricular origin. In *CASE 2*, a patient subject to numerous tachycardial paroxysms arising in the auricle, the passage of a paroxysm of this form into auricular fibrillation was observed and is shown in Fig. 7.*

9. The frequent association of auricular fibrillation with mitral stenosis and rheumatic heart disease is now a well recognised fact. In our own series, which comprises twelve cases of paroxysmal tachycardia of auricular or supraventricular origin, five were cases of mitral stenosis and in one of the remaining seven cases there was a history of rheumatic fever. We cite these figures for the purpose of showing that regular tachycardias and fibrillation are met with in a common class of cases.

While we divide heterogenetic impulse formation into three grades, the isolated premature beat, regular tachycardia and auricular fibrillation,

* Two new instances of the passage of regular paroxysms of tachycardia of auricular origin into auricular fibrillation have been observed by one of us, since these pages were written.

the division is an arbitrary one, and transitions from one stage to another occur and have been already referred to. Hewlett's case is a notable instance. *CASES 1* and *2* of the present communication may also be cited in this connection. In *CASE 1*, the regular paroxysm was interrupted by premature beats, which presumably were also of auricular origin, although they were not recorded electrocardiographically. *CASE 2* provides a clear instance of the transition. Paroxysms of regular tachycardia, generated in an ectopic focus, are interrupted by single beats, most of them premature in relationship to the paroxysm itself, springing from a separate ectopic focus. The presence of two active extraneous foci of impulse formation in the auricle, and the ultimate passage of a paroxysm into fibrillation in this patient, has a peculiarly significant bearing upon the question of the production of auricular fibrillation from multiple auricular foci. Whether the short period of irregularity recorded in Fig. 7 (at the point *B*) is a further transition or not we are unable to ascertain positively in the absence of the corresponding electrocardiogram, but we believe this to be the case.

We may sum up the previous discussion in the statement that there is a rapid accumulation of evidence, which shows the close association of the modes of genesis of three forms of disturbance of the normal cardiac rhythm, namely, premature contractions, paroxysms of regular tachycardia and fibrillation. The hypothesis represents the relation in more tangible form; the three forms of disturbance may be regarded as the expression of heterogenetic or pathological impulse formation of three grades, the production of single and isolated impulses, the occurrence of a series of impulses from a single focus and finally the activity of a number of such foci.

It is perfectly true that certain cases show one or other mechanism alone. It is also true that the connecting links in the individual case are often imperfect or absent; thus, cases of auricular fibrillation may apparently show intervening periods of slow and normal heart action which are perfectly regular. It is possible, nay probable, that records of the actual passage of normal mechanism to fibrillation in these last cases will ultimately reveal transitions, but we freely admit the possibility that such transitional curves may not occur, and that the changes may be abrupt from one to the other. An abrupt change from auricular fibrillation to a normal mechanism is indeed the rule in experiments upon healthy hearts, but we cannot see that these observations appreciably affect our general contention.

SUMMARY.

1. Two instances of paroxysmal tachycardia are recorded. In the first case, the paroxysms usually consisted of auricular fibrillation; on one occasion, at least, the passage of the fibrillation into a regular tachycardia

of ectopic auricular origin was observed. In the other instance, the paroxysms consisted of tachycardia of ectopic auricular origin; on one occasion the passage of such a tachycardia into fibrillation and the subsequent resumption of the normal rhythm, interrupted by regular paroxysms, was observed.

2. The regular tachycardias in these two cases were interrupted by premature contractions, which in one case probably, and in the other case certainly, came from a separate and ectopic auricular focus. The significance of this observation and its relation to the passing of regular tachycardia into fibrillation is discussed.

3. A detailed account of the evidence, which leads us to the view that the single premature contraction, ectopic tachycardia and fibrillation have a similar pathogenesis, is given.

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- ⁴ LEVY & LEWIS. *Heart*, 1911, III, 99.
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- ⁶ LEWIS. *Heart*, 1909, I, 98.
- ⁷ LEWIS. *Heart*, 1909, I, 262.
- ⁸ LEWIS. *Heart*, 1910, I, 306, (Case 10, 11 and 15, and Fig. 9).
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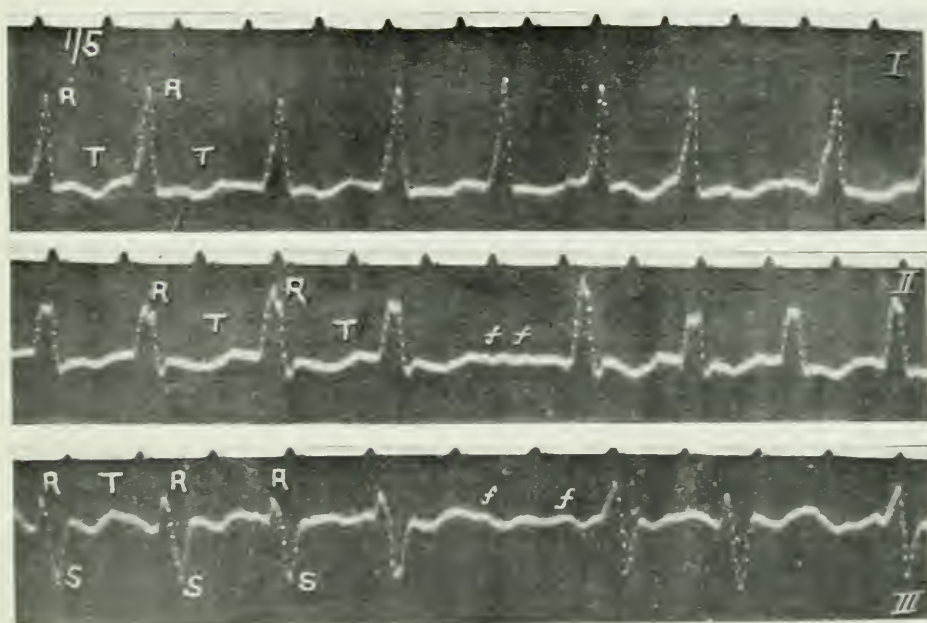


FIG 10

Fig. 8, 9 and 10. *CASE I.* Three series of curves from a case of paroxysmal tachycardia, showing separate mechanisms. Each series comprises the three customary leads: right arm to left arm (*I*), right arm to left leg (*II*), and left arm to left leg (*III*). In each series lead *II* is standardised, so that 1/1000 volt = 0.6 centimetres in the reduced curve.

Fig. 8. Showing the mechanism of the heart on June the 1st, 1911, when the pulse was regular and when its rate was 65 per minute. The *P-R* interval is .14 sec. The time-marker is in 1/30 sec. (June the 1st, 1911).

Fig. 9. Showing the mechanism on July the 2nd at the end of the long paroxysm. The heart beats are regular, at the rate of approximately 140. The ventricular complexes are of the type induced by supraventricular impulses; each is preceded by an anomalous auricular complex *P*. The *P-R* interval is 0.18 sec. The time-marker is in 1/5 sec. (July the 2nd, 1911).

Fig. 10. Showing the mechanism on July the 1st, shortly after the onset of the long paroxysm. The beats are irregularly placed; the rate reaches 193 per minute. The ventricular complexes are all of the type attributable to supraventricular impulses. Co-ordinate contractions of the auricle are not represented. *P* is replaced by the oscillations (*f*) which characterise fibrillation of the auricle. The time-marker is in 1/5 sec. (July the 1st, 1911).

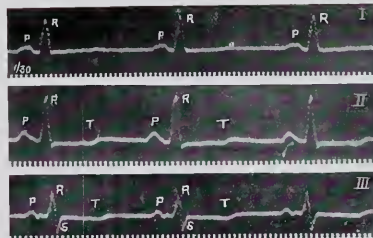


FIG. 8.

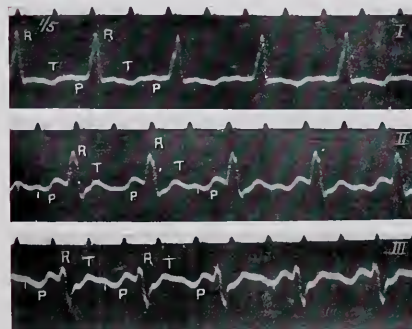


FIG. 9.

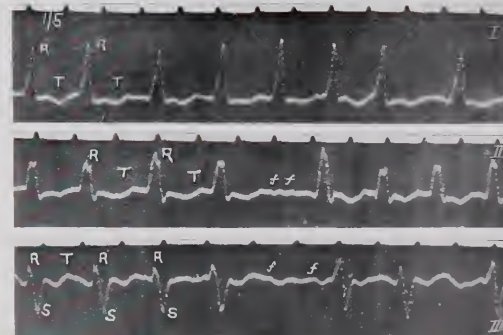


FIG. 10.



FIG. 15.

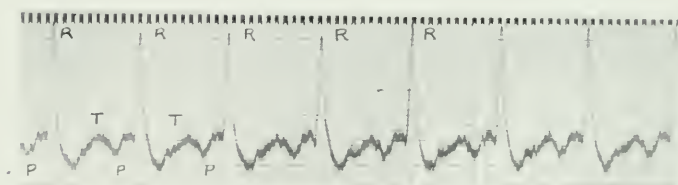


FIG. 16.

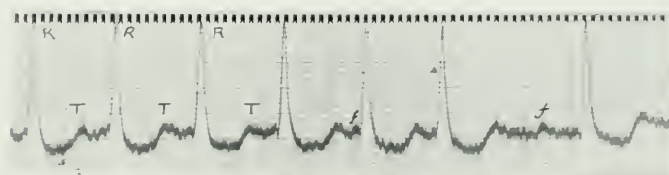


FIG. 17.

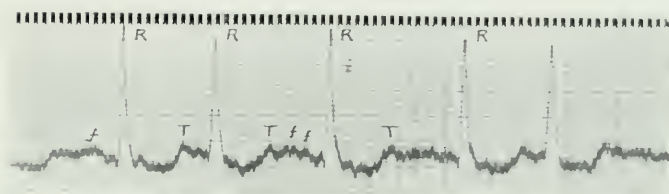


FIG. 18.

Fig. 11-14. CASE 2. A series of curves taken on July the 4th, 1911. The time-marker is in 1.30 sec..

Fig. 11 shows four beats of the normal rhythm, each cycle consisting of *P*, *R* and *T* variations. The amplitude of *R* is variable.

Fig. 12. A curve taken from a slow period and showing a single premature contraction, arising from an ectopic auricular focus. The premature auricular representative is marked *P* below the curve.

Fig. 13. A curve taken during an auricular paroxysm showing inverted *P* waves. The last cycle but one is constituted by a beat arising from a second focus, as is shown by the shape of the auricular representative marked *P'*. Note the variation in the amplitude of *R* in this figure.

Fig. 14. The end of a regular paroxysm of the same type. Two beats of the usual paroxysmal form are shown. The third beat ends the paroxysm and arises, as shown by the shape of *P'*, from a second abnormal focus. The post-paroxysmal pause and the resumption of the normal rhythm are seen.

Fig. 15. CASE 2. Taken on June the 27th, 1911, and showing a single premature auricular contraction which springs from the same focus as the majority of the paroxysmal beats. The time-marker is in 1/5 sec..

Fig. 16-18. CASE 2. A series of curves taken on July the 18th, 1911. Fig. 7 covers the same period of observation. The time-marker in all three curves is in 1.30 sec..

Fig. 16 was taken shortly after the onset of a regular paroxysm. The type of paroxysm is similar to that shown in Fig. 13.

Fig. 17 was taken almost directly afterwards. It shows no evidence of a co-ordinate auricular contraction; the heart-beat is quite irregular and oscillations characteristic of auricular fibrillation are present (*f*, *f*).

Fig. 18. A similar curve taken later during the same attack, and showing the characteristic picture of auricular fibrillation.

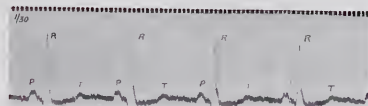


FIG. 11

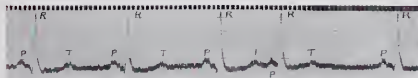


FIG. 12.

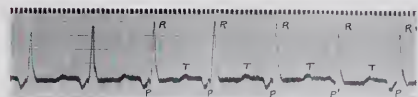


FIG. 13.

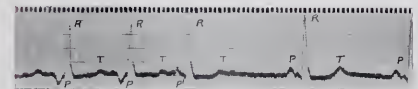


FIG. 14.



FIG. 15.

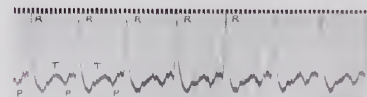


FIG. 16.

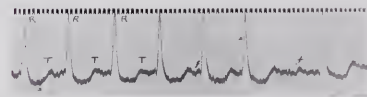


FIG. 17.

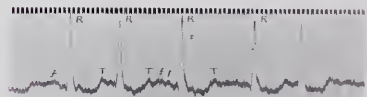


FIG. 18.

ACUTE CARDITIS AND HEART-BLOCK.

By H. G. BUTTERFIELD.

(*University College Hospital Medical School*).

F. K., girl aged 16 years, was admitted to the City of London Hospital for Diseases of the Chest on May the 26th, 1911.

History.—There was no history of heart disease or of rheumatic fever in the family. The patient contracted measles in infancy and had suffered from time to time with pain between the shoulders. There was no history of acute rheumatism, scarlet fever, whooping cough, pneumonia or chorea.

Five weeks before admission she complained of palpitation, pain in the chest and back after food, and pain in the knees.

She attended the Out-Patient Department for two weeks. On May the 12th, Dr. Riviere found that the heart was dilated and observed a systolic murmur of mitral origin. He advised the mother to leave the girl in the hospital.

She was finally persuaded to come into the hospital on May the 26th as the symptoms had become more marked. The patient was now seriously ill with pain in the left side, sleeplessness and shortness of breath. There had been cough and expectoration for one week.

State on admission.—The patient was anæmic, the tongue was slightly coated. The pulse rate was rapid, 132 per minute, regular and dicrotic. The heart's apex beat was in the fifth space, one inch external to the nipple line. There was a large extension of dulness to the right of the sternum. A systolic murmur was present at the apex, and over the sternum a well marked pericardial rub was heard. There were also friction sounds over the bases of both lungs at the back. In the same situation flatness of the percussion note was present. The urine was normal.

On the 27th the condition remained unaltered; the pulse was rapid, but the mechanism of the heart was normal (Fig. 1).

On May the 28th, some cyanosis was noted; the respirations had increased from 24 to 28 per minute and were embarrassed. The left border of dulness was then two inches outside the nipple line, the upper border was at the upper border of the third rib. There were loud systolic and rumbling diastolic bruits in the mitral area, the aortic sound was only faintly heard. The pulmonary and tricuspid sounds were normal. The friction was still present. There was bronchial breathing at the right apex, moist crepitations at both apices and well marked dulness over both bases, more especially over the right. Breath sounds over the right base were almost completely absent. Rales were heard on both sides.

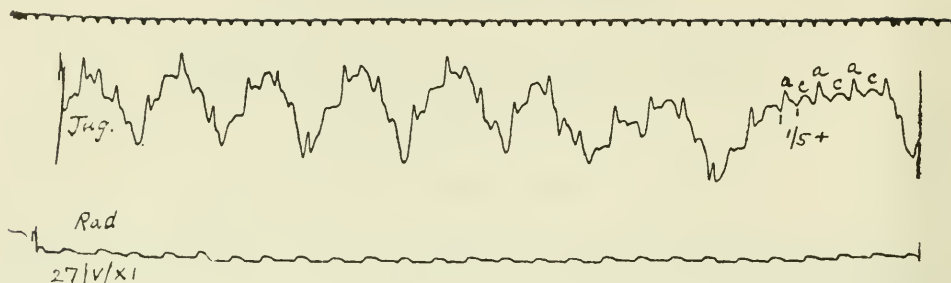


Fig. 1. A polygraphic curve taken on May the 27th. The radial pulse is rapid and irregular. The jugular curve shows marked respiratory excursions, except at the end of the tracing, where breathing ceased. The *a* waves are clear for three cycles and the *a-c* interval slightly exceeds one-fifth of a second.

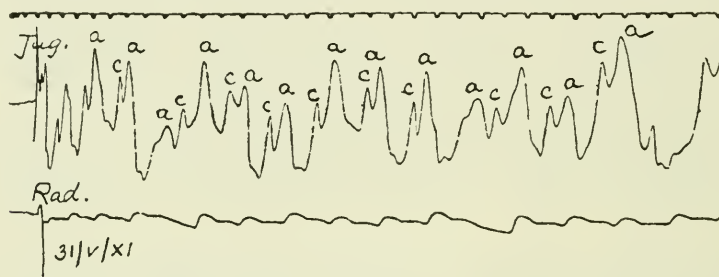


Fig. 2. A polygraphic curve showing two dropped beats. The *a-c* intervals show progressive increase up to the point at which these beats are dropped. The longest interval is approximately $1\frac{1}{5}$ second. (May the 31st.)

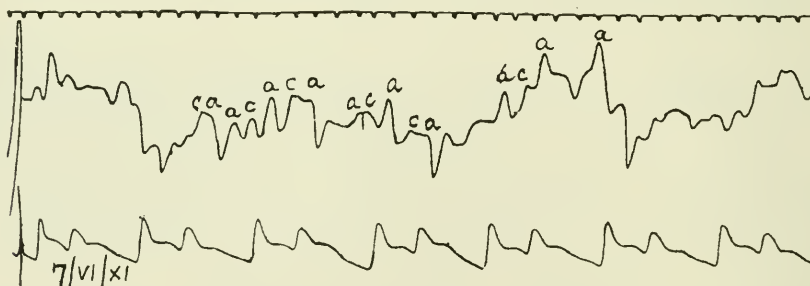


Fig. 3. A polygraphic curve taken on June the 7th. A ventricular response is lost after each third auricular contraction.

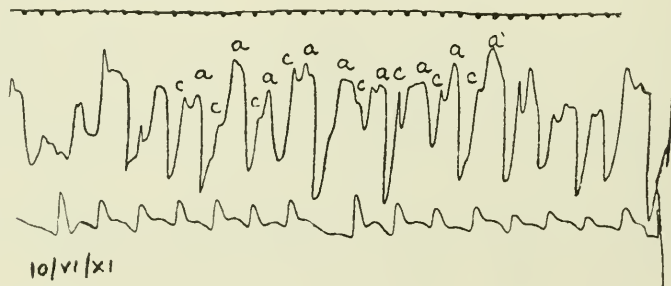


Fig. 4. A polygraphic curve taken on the day of death. It shows occasional dropped beats. (June the 10th.)

On May the 30th, the pulse was first noticed to be irregular; the irregularity was due to partial heart-block, and consisted of occasional pulse intermissions.

On May the 31st, the blocked beats were still present (Fig. 2). The physical signs in the chest remained practically unaltered.

On June the 1st she received digitalis in 10 minim doses of the tincture and this was continued until June the 5th. Dropped beats were present throughout the whole of this time and the patient showed considerable improvement, in so far as her symptoms were concerned, up till the day on which the digitalis was discontinued, when she became more dyspnoëic and cyanosed.

On June the 7th, one beat in three was missed (Fig. 3), and on the 8th, a pause occurred after each third or fourth beat; on these days, tubular breathing was heard in the right axillary region. Pericardial friction was still present, but was not so audible.

During the stay of the patient in hospital, the temperature was intermittent, ranging from 97-100 degrees Fahrenheit. The pulse rate varied from 80-136; the respirations from 24 to 48. The urine flow was plentiful throughout.

The dropped beats continued till the time of death (Fig. 4), which occurred on June the 10th at 6.15 p.m. The post-mortem was held at 2.30 p.m. on the 12th.

Post-mortem.

The body is that of a well nourished girl. The œsophagus and trachea, the cervical and bronchial glands appear healthy. In the right pleural sac there is a quantity of clear yellow fluid; a little is also seen in the left cavity. The lungs (right, 17 oz., and left, 15 oz.) are somewhat œdematous and there are patches of collapse in the right organ. The pericardium is loosely adherent; recent adhesions, readily separated, are present, and there is no excess of fluid. The epicardium is covered with a semiplastic exudate.

Heart.—The weight with the pericardium is 22 oz.; the weight without the pericardium 15½ oz.. The muscle is soft, friable and pale. There is no evidence of fatty change. The left ventricle is markedly dilated. The mitral valve exhibits a series of recent vegetations near the flap margins. The ring is not narrowed. The aortic valve is studded with small recent vegetations along the borders of the cusps. The valve is incompetent. The right ventricle shows dilatation. There are a few fresh vegetations on the tricuspid valve margins, and there is an extensive accumulation of ante-mortem clot around the valve curtains. The pulmonary valves are healthy.

The liver weighs 57 oz., and is engorged. The kidneys weigh 8½ oz. together and have a healthy appearance. So also has the spleen, which weighs 6½ oz.. The remaining abdominal organs are normal. No secondary abscesses are to be found.

Microscopic examination of the heart.

The heart had been fixed in Formol-Muller solution. This was washed out as far as possible and the remainder of the fixation carried out in a solution of four per cent. formalin in normal saline. The area containing the auriculo-ventricular node and bundle was excised. All were hardened and dehydrated in absolute alcohol, passed through carbon bisulphide and thence embedded in paraffin with a melting point of 52° Centigrade. Two pieces of tissue were removed from the centre of the external wall of each of the chambers of the heart, in planes parallel and at right angles to the surface. Portions of the valves and the thickened pericardium were also taken. The sections of the node and bundle were cut in series, every fifth being mounted. The sections were cut 12 micromillimetres in thickness, with an occasional thin one at regular intervals to obtain minute histological detail, and were stained with Ehrlich's acid hæmatoxylin and van Gieson's solution; the sections from the remaining blocks of tissue were of varying thickness and were stained with hæmatoxylin and eosin, hæmatoxylin and van Gieson's solution, the methyl green and pyronin mixture of Pappenheim and Mann's methyl-blue eosin mixture. The bacteriology was studied mainly in the valves, the methods used being the Eosin-Gram-Weigert procedure for the Gram staining organisms and Zieler's method for the bacteria in general.

Frozen sections were also cut from various parts of the heart and stained for fat with Scharlach R in acetone-alcohol solution, control tissues known to be fatty being used in all cases to verify the staining properties of the reagent. Repeated attempts to demonstrate fatty particles in the muscle fibres had negative results.

Bacteriological examination showed the presence of numerous Gram-positive diplococci with a tendency to short chain formation and in some cases to only partial retention of the methyl violet stain used. Some of these organisms were very small and in general they were smaller than the ordinary streptococcus pyogenes. No capsulated organisms were found and the examinations by Zieler's method gave the same results as that for Gram positive bacteria.

Histologically the cardiac muscle fibres were normal in appearance and showed the usual transverse striation perfectly well throughout.

The sections examined from the external wall of the *right ventricle* showed a slight general increase in the connective tissue elements and fairly well marked perivascular infiltrations, which were almost entirely lymphocytic in character with an occasional large mononuclear cell. The muscle immediately under the epicardium seemed unaffected by the proliferation of the connective tissue elements consequent on the pericarditis, a statement which holds good in the case of the ventricular wall on the left side as well as on the right.

The sections of the external wall of the *left ventricle* showed a small general increase in the connective tissue elements and small perivascular infiltrations which differed somewhat from those on the right side in that they contained a constant small proportion of polymorphonuclear leucocytes. Among the newly formed connective tissue on the surface of the ventricle a well marked giant cell lesion, in connection with a vessel and surrounded by a lymphocytic and large mononuclear infiltration, was found. Except that it occurred in obvious association with a vessel and that no leucocytes were found in the infiltration, it corresponded in all respects with the valvular lesion depicted in Fig. 5 which is fully described below.

In the *right auricle* a considerable increase in the connective tissue elements was found with extensive perivascular infiltrations of lymphocytic character. In the thickened epicardium of this region some single giant cells were seen. They had the same staining character as those described below in connection with the valves, interauricular septum and bundle, and they were in close relationship with vessels. The accompanying infiltrations were mainly lymphocytic with an occasional leucocyte.

The sections of the external wall of the *left auricle* showed perivascular infiltrations, especially marked at the surface, and a greater increase of young connective tissue than any other part of the heart examined. Giant cells were found in the thickened epicardium and several very large mononuclear cells occurred in the surrounding infiltrations which also showed leucocytes and lymphocytes.

The *auriculo-ventricular node* was deeply involved in the morbid process, particularly in the neighbourhood of the central fibrous body, where the normal appearances were completely obscured by a dense cellular infiltration of lymphocytes, leucocytes and large mononuclear cells. Throughout the remainder of the node and bundle, with the exception of the right branch, every vessel was surrounded by an infiltration composed almost entirely of lymphocytes. The infiltration in the neighbourhood of the central fibrous body contained a much larger proportion of polymorphonuclear leucocytes than any of the infiltrations in other parts of the heart, except those in the immediate neighbourhood of the giant cell lesions in the interauricular septum and the valves. The appearance of the node in the neighbourhood of the central fibrous body is shown in Fig. 7 which is a reproduction of a microphotograph taken from that region.

No giant cells or other large cells having similar staining reactions were found in any portion of the node proper. The *right branch* of the bundle was unaffected; the *left branch*, on the other hand, was surrounded by infiltrations throughout the whole of its traced course under the surface of the left ventricle. In addition to the infiltrations, which shared the general characteristics described in connection with the perivascular phenomena, the giant cell lesion which is shown in Fig. 8 was discovered in the fibrous sheath in close proximity to the fibres of this branch of the bundle. There seemed

to be some diminution in the size of the fibres at this point ; but the changes were not conspicuous and the surrounding infiltration, which was such a marked feature in the other two giant cell lesions from which illustrations are given, consisted in this region of a very few lymphocytes and polymorphonuclear leucocytes.

Fig. 6 is a drawing of a large collection of giant cells found close under the endocardium of the left auricle in the interauricular septum and well above the level of the upper portion of the node. This cell group formed a band of tissue at right angles to the internal surface of the auricle and lay close to apparently normal cardiac muscle. Its constituent cells call for no separate description, since they were similar to those of the valve lesion subsequently described. A few other groups of cells were seen having a similar arrangement and similar staining reactions but only single nuclei. These occurred well towards the left side of the interauricular septum deep in the sub-endocardial connective tissue. On the right side of the septum throughout the series there were groups of cells having from one to three nuclei ; from their staining properties they seemed to be of the same nature. Their presence was unassociated with lesions of the endothelium except at two points where local destruction had evidently taken place.

The valves showed considerable thickening, recent vegetations and numerous localised areas denuded of endothelium and covered by recent fibrinous deposits. The substance of the valves was completely vascularised ; in all segments of the mitral, aortic and tricuspid valves giant cell lesions were seen in all stages of formation. One of these valvular lesions is shown in Fig. 5 which is a drawing of a portion of the posterior aortic cusp. The giant cells in this and the other situations stained very deeply with the combination of hæmatoxylin and van Gieson used for the serial sections and their multinucleate character was difficult to establish under a low power of the microscope. The nuclei were either heaped together in the centre of the cell or evenly distributed in the protoplasm, but showed no tendency to arrangement round the cell periphery as in tubercular giant cells. The periphery of each individual nucleus stained very deeply with the hæmatoxylin and a densely staining chromatin mass of irregular size and shape was usually visible in the centre, leaving the remainder of the nucleus clear or showing only a few fine fibrils of chromatin substance so arranged as to give the appearance of a loose meshwork. The protoplasm around these nuclei had a marked affinity for alkaline dyes and stained deeply with hæmatoxylin. None of the giant cells in the heart or pericardium showed necrosis, though some stained more deeply than others ; as the latter were found among connective tissue which appeared more mature than that in which the deeply stained forms were observed, it is possible that the more faintly staining forms represented a later stage in development.

The particular lesion shown in Fig. 5 showed no connection with any vessel nor did the other similar lesions, with the exception of the examples which occurred in the thickened epicardium over the left ventricle and the right auricle. The lesions obviously associated with vessels took the stain deeply.

Large cells in groups of from four to twenty, and possessing single nuclei, were found in the neighbourhood of the multinucleate cells. They differed from the giant cells in size and numbers of nuclei only. There were many of such groups in the valves, both in the highly vascularised connective tissue and immediately underneath fibrin-capped lesions of the endocardium. In working systematically through a score of these groups all gradations from an enlarged connective tissue cell to a small giant cell with two or three nuclei seemed apparent.

On the whole these lesions correspond with those described by Aschoff and Tawara ¹ and ², and by Carey Coombs³ in this country, as occurring in acute rheumatic infection of the heart.

My thanks are due to Dr. Thomas Lewis for the opportunity of publishing the case and for the use of the clinical notes and curves.

SUMMARY.

A case of acute infection of the whole heart, including its membranes, is described.

Partial heart-block supervened eleven days before death, and continued until that event took place.

Histological examination of the heart showed the presence of a widely diffused inflammatory infiltration, conspicuous in the region of the central fibrous body and reaching its greatest intensity in the auriculo-ventricular node, where that structure lies in proximity to the central fibrous body.

The infection was a uniform one by Gram-staining organisms which were non-capsulated diplococci tending to form short chains and occurring more especially in the valves, epicardium and pericardium.

The nature of the inflammatory reaction was similar to that described by Aschoff and Tawara as being characteristic of rheumatic infection.

The lesions consisted chiefly of lymphocytic infiltrations; though polymorphonuclear leucocytes were also present in the node and around certain specialised cellular lesions.

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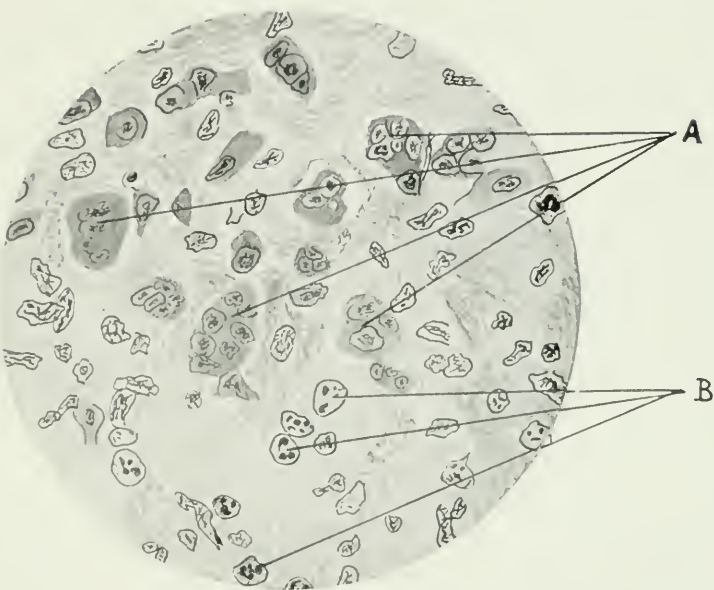


FIG. 6.

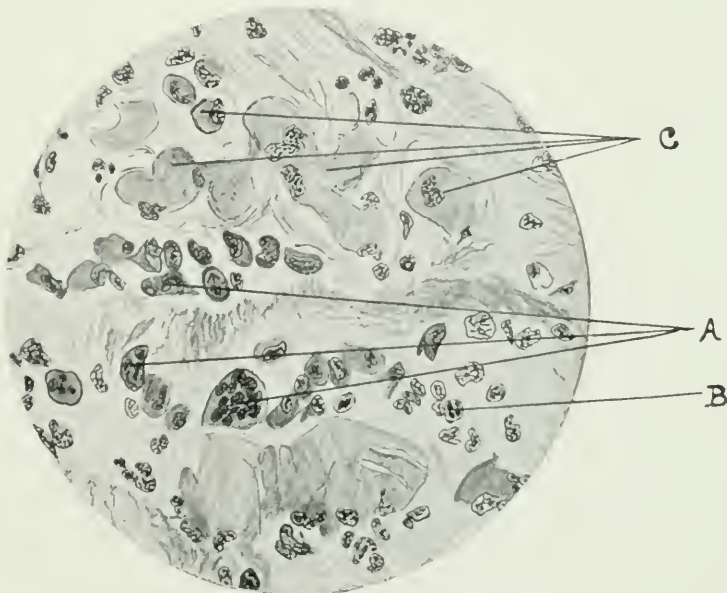


FIG. 8.

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Fig. 5. A camera lucida drawing of a group of giant cells found in the thickened posterior cusp of the aortic valve. *A*, multinucleate cells and large cells of similar form, except that their nuclei are single. *B*, polymorphonuclear leucocytes which in this instance are a marked feature in the surrounding cellular infiltration. $\times 500$.

Fig. 6. A drawing of a similar lesion found under the endocardium on the left side of the inter-auricular septum. The magnification is the same as in Fig. 5 and the letters refer to the same points.

Fig. 7. A microphotograph of the auriculo-ventricular node showing the mixed cellular infiltration which at this point obscures the normal tissue arrangement. The magnification is approximately 45 diameters.

Fig. 8. A drawing of a giant cell lesion on the course of the left branch of the bundle. The letters *A* and *B* have the same references as in Fig. 5 and 6. The letter *C* indicates muscular fibres of the bundle. 500.

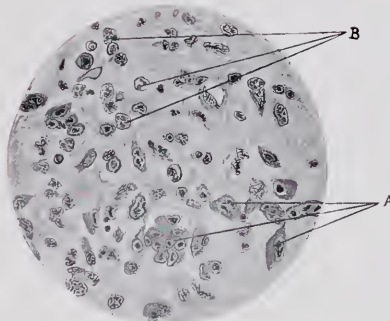


FIG. 5.

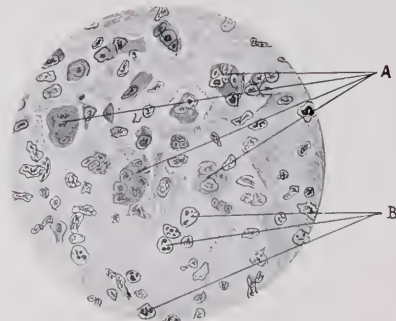


FIG. 6.

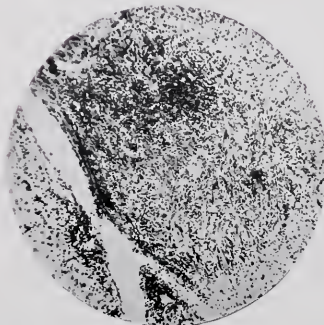


FIG. 7.

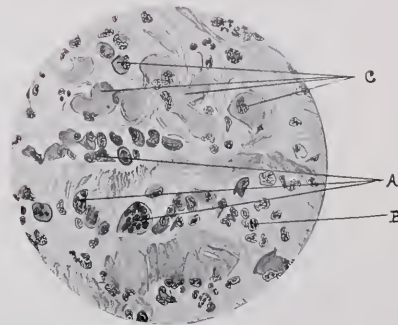


FIG. 8.

XI. The Human Electrocardiogram: a Preliminary Investigation of Young Male Adults, to form a Basis for Pathological Study.

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Communicated by Sir J. R. BRADFORD, Sec. R.S.

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[PLATES 19 AND 20.]

The adoption of the galvanometer and its employment for clinical purposes dates from the introduction of the newly modelled instrument or string galvanometer by EINTHOVEN.

The string galvanometer has proved an efficient instrument in deciphering all forms of irregularity of the ventricle, and has given clear interpretations of all derangements of the heart in which there is disorder in the sequence of contraction in its chambers. This new chapter of clinical medicine is rapidly closing, but while it has been written, a number of isolated observations have been placed on record, from which it is clear that the instrument may be employed for a further purpose. It is probable that it will give information of much value where the action of the heart, as a whole, is perfectly regular, and where the contraction, originating at the normal site of impulse formation, namely, the sino-auricular node, progresses at normal rates through the heart and along definite and recognised channels. Thus, it is known that in certain instances of cardiac enlargement some of the electric variations portrayed in the curves are exaggerated, decreased, or inverted, as compared to the normal and to each other. But it is evident that little progress can be made in the study of this subject until we have full knowledge of the normal electrocardiogram, and especially of the limits which may be reached by its several peaks and depressions in healthy subjects. As an initial step towards this end we have examined the curves of a large number of healthy young adults.

METHODS ADOPTED.

For the purposes of this investigation we have taken the material which has been at hand, namely, medical students of healthy aspect, whose ages ranged from 18 to 35 years. We wished to collect the electrocardiograms of 50 or more such subjects, and in taking an actual total of 59 subjects,† we have rejected seven. The reasons for

* Working under the tenure of a Beit Memorial Research Fellowship.

† The actual number of observations, described in this communication, does not represent the whole of the material studied. We decided that it was desirable for the purposes of the investigation to commence with a clean slate, using the experience of the past simply as a guide to our work.

the rejection of these seven subjects will be fully stated when the normal curves have been considered.

The records have been taken by means of Edelmann's pattern of Einthoven's string galvanometer (No. 1500 in Edelmann's Catalogue). The magnet of this galvanometer is an electromagnet, and the string employed in the present work has been a platinum fibre having a resistance of 11,600 ohms. The routine adopted in the examination of any given subject is that of EINTHOVEN, and is described in his paper in the 'Archives internationales de Physiologie,' 1906, vol. 4, p. 132. The curves are taken from three leads—right arm to left arm, right arm to left leg, and left arm to left leg, henceforth termed leads *I*, *II*, and *III* respectively.

Estimation of Resistance.

The subjects sit in easy and uniform positions,* and the leading-off electrodes are attached to the three limbs, any pair of which may be selected at the main switch board. The resistances of the separate leads are estimated by means of a telephone and Wheatstone's bridge. The instrument employed for this purpose gives readings to within 50 ohms of the resistance tested,† an approximation which is more than sufficiently accurate for our purposes. The actual resistances, as measured, have lain between 300 and 900 ohms.

Standardisation of the Instrument.

The resistance being ascertained, a corresponding quantity is thrown into the galvanometric circuit. In taking some of the earlier records, we maintained a uniform resistance of 21,600 ohms in the circuit, measuring the resistance of the subject in each instance and adding to it the quantity necessary to bring the total to 21,600 ohms. The total resistance was established by the string of 11,600 ohms and by an added resistance of 10,000 ohms. This method was adopted because it necessitated fewer tests of the excursion of the string, when a current of definite strength was passed through it, and several subjects might be observed in rapid sequence without further alteration of the string tension. But later we found that so large an internal resistance reduces the sensitivity of our instrument to a point which is inconvenient for all observations, and we consequently discarded the method in favour of standardisation on each occasion with a resistance equivalent to that of the patient alone in circuit with the string.

Eventually we instituted a careful comparison of the two methods, namely, standardisation of the string with (1) an added resistance of 10,000 ohms, including

* We have made a number of observations upon the effect of posture, to determine the uniformity of position which it is necessary to maintain in order to secure uniformity in the curves. Small deviations from a given posture are without significance.

† This approximation is safe because of the high total resistance, usually more than 12,000 ohms, in the galvanometric circuit.

the resistance of the patient, and with (2) an added resistance equivalent to the resistance of the subject. This comparison has yielded results of value, which will be referred to in more detail in succeeding paragraphs.

The instrument is standardised by throwing an accurately measured potential of 3 millivolts, from a Weston normal cell, into the galvanometric circuit, and by altering the tension of the string until a deviation of exactly 3 cm. is obtained. The excursion obtained by $\frac{1}{1000}$ volt, namely, 1 cm., is checked immediately after the electrocardiogram is taken, the record usually lying on the same plate (figs. 1, 12, and 14). All the measurements of curves referred to in the present communication have been made from the horizontal lines which are ruled photographically upon the plates at intervals of 1 mm. These lines are seen in the figures and for the convenience of measurement the ruling is so arranged that each fifth line is somewhat thicker than the remainder.

Estimation of the Deflection Time of the String.

It is very essential, if the curves are to accurately represent the variations in the strength of the current flowing through the string, that the deflection time of the string should be accurately ascertained and graduated according to the rate of change in the strength of the currents tested. For human electrocardiographic work, SAMOJLOFF* states that the deflection time should not exceed 0.03 sec. From our past experience we know that deflection times of greater magnitude certainly produce distortion of the curves, distortion which is always present, when the time amounts to 0.06 sec. or less. But it was thought desirable that the limit of safety should be more accurately defined.

The deflection time of the string varies with the amplitude of excursion; the greater the amplitude, the longer the time, though the change is not proportional. In speaking of a deflection time of 0.03 or 0.06 sec., a deflection time of a string shadow which passes over a distance of 1 cm. is understood. Now, if the exact outline of a normal electrocardiogram is known, the safe maximal limit for the deflection time, for the particular subject and lead, may be estimated by measuring the time duration of the quickest deflection in the curve itself. Thus, in fig. 1A, the line joining the apices of *R* and *S* is the most vertical in the curve. The actual duration of the swing from the point of *R* to the point of *S* is approximately 0.023 sec. Consequently the maximal limit of the deflection time which it is safe to employ in obtaining a perfect representation of the current changes in this instance should be 0.023 sec.; for the total excursion from the top of *R* to the bottom of *S* is 10.5 mm., or approximately 1 cm. And the adoption of any deflection time of lesser magnitude than 0.023 sec.† should yield a curve which is identical with fig. 1A in measurements and general outline. That this is actually the case may be seen from the remaining

* "Elektrokardiogramme," 'Sammlung anatomischer und physiologischer Vorträge und Aufsätze,' Gaupp and Nagel, Jena, 1909.

† Always providing that the limit of overtightness of the string is not reached.

TABLE I.

	<i>P.</i>	<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	Deflection times.
						sec.
Fig. 1 <i>A</i>	1.0	0	6.5	4.0	4.0	0.013
Fig. 1 <i>B</i>	1.0	0	6.5	4.0	4.0	0.023
Fig. 1 <i>C</i>	1.0	0	6.0	3.0	4.0	0.028
Fig. 1 <i>D</i>	1.0	0	5.5	3.0	4.5	0.045
Fig. 1 <i>E</i>	0.7	0	4.7	1.7	4.5	0.060
Fig. 1 <i>F</i>	0.7	0	4.0	1.3	4.5	0.070

A tabulated statement of the measurements of the curves in figs. 1*A-F*.

curves of the same figure. The deflection times corresponding to figs. 1*A* and 1*B* are 0.013 and 0.023 sec. respectively. The corresponding curves are alike in every respect, but as soon as the limit of safety, in this instance 0.023 sec., is passed, alterations are noticed in the curves: the first change is in the amplitude of the depression *S*. Thus in fig. 1*C*, taken when the string gave a deflection time of 0.028 sec., or $\frac{5}{1000}$ sec. beyond the calculated limit of safety, a shortening of *S* from 4 mm. to 3 mm. occurs, while, with the exception of a slighter reduction in *R*, the remainder of the summits practically retain their original measurements and outlines.

To complete the illustration, we publish three further curves in which deflection times of 0.045, 0.060, and 0.070 sec. were employed. The curves show more and more distortion. *R* and *S* gradually become reduced in amplitude, as they are traced from above downward through the series. These are the peaks which suffer most. *P* is slightly reduced in amplitude in the last two curves, figs. 1*E* and 1*F*, while *T* shows a slight but appreciable increase in figs. 1*D*, 1*E*, and 1*F*.*

In our observations upon students, we have adopted deflection times which we know from experience to be at or near the maximal limit of safety, on a number of occasions, and we have compared the curves thus obtained with the curves given while using deflection times of lesser magnitude. In making such observations two complete photographs are taken in quick succession; each consists of curves from the three leads, and the measurements in the two photographs are subsequently compared. The comparisons will be found in Table III, wherever two curves from the same subject are charted under one date.

To illustrate the curves we publish figs. 12 and 14, from a subject in whom the desired deflection time is small; they were taken within a few minutes of each other. The deflection time for fig. 12 is 0.012 sec., and for fig. 14, 0.022 sec. The general outline of the curves from the three leads is well maintained in the two photographs. The differences in measurements are minute, but are in many ways characteristic of the slight distortion of curves which occurs at or about the deflection times

* The illustration is but an example of a number of serial observations.

TABLE II.

No.	Initials.	Deflection times.	Losses.	Gains.
1	C. E. S.	0·016 0·021	R^2 from 15 to 14	
7	C. E. A. G.	0·016 0·025	S^2 from 3·5 to 3 R^3 from 12 to 11	T^3 from 1 to 1·3.
11	J. M. E.	0·018 0·028		No differences.
12	H. C. G. P.	0·013 0·021		R^2 from 12 to 12·5. T^1 from 2·5 to 3·0.
14	G. G. A.	0·012 0·022	S^1 from 3·5 to 3 S^2 from 1 to 0 S^3 from 1 to 0·5 R^2 from 13 to 12 R^3 from 11 to 10	R^1 from 3·5 to 4. T^1 from 1·3 to 2. T^2 from 3·0 to 3·5.
20	L. B. C. T.	0·013 0·016		No differences.
27	A. P.	0·016 0·023	S^1 from 1 to trace S^2 from 1·5 to 0·5 S^3 from 1 to 0. R^3 from 5 to 3·5 Q^2 from 1 to 0·7 T^3 from 0·5 to trace	R^2 from 8·5 to 9·5. Q^3 from 1 to 1·5. T^1 from 2 to 2·5. T^2 from 2·5 to 3·5.
29	C. McI.	0·018 0·025	S^2 from 2 to 1 S^3 from 2 to 1·3	R^1 from 4·5 to 5·0. T^1 from 1·0 to 1·5.
42	H. D.	0·010 0·020	R^2 from 9 to 8·5	
48	E. B. J.	0·013 0·021		P^2 from 0·7 to 1. Q^2 from 0·5 to 1. R^2 from 8·5 to 9. There were also gains in the bracketed Q , R , S deflection of leads <i>III</i> .
51	R. H. L.	0·016 0·020	R^1 from 5·5 to 5 S^2 from 4·0 to 3·5 S^3 from 4 to 3 T^1 from 2·7 to 2·3 T^2 from 2·5 to 2	
59	P. V. E.	0·013 0·023	S^2 from 2·0 to 1·5 T^2 from 3·5 to 3	

A table showing the alteration in the amplitude of the summits and depressions, when deflection times of 0·010–0·018 sec. are replaced by deflection times of 0·016–0·028 sec. A number of the gains and losses, especially those which fall upon Q and R , are no more than are to be accounted for by natural variation in the amplitudes of these deflections from time to time.

0.020–0.025 sec. For example S^1 is reduced from 3.5 mm. to 3 mm.; S^2 is reduced from 1 mm. to 0 mm.*; S^3 is reduced from 1 mm. to 0.5 mm. R^3 is also reduced from 11 mm. to 10 mm., and R^2 from 13 mm. to 12 mm. On the other hand R^1 is increased from 3.5 mm. to 4 mm.,† T^1 gains from 1.3 mm. to 2 mm., and T^2 from 3 mm. to 3.5 mm.

The comparison has been instituted in 12 instances, using smaller deflection times, which varied from 0.010 sec. to 0.018 sec., and longer deflection times varying from 0.016 sec. to 0.028 sec. The quantities of loss or gain in the summit R and in the depression S must be surveyed in the whole series, for the variation in the size of these peaks from beat to beat introduces a slight error into many such calculations. The losses and gains in the whole series are given in the accompanying table (Table II). It will be seen that the gains, in so far as they affect R and Q , are small in number and inappreciable in extent. They fall upon Q^3 , R^1 , and R^2 .‡ There is a frequent slight gain in T , especially in T^1 . S shows no gain. The losses are numerous though inappreciable in extent. The most conspicuous losses are in S^2 , S^3 , R^3 , S^1 , and R^2 , in this order.

The modifications produced in the electrocardiogram, when deflection times of magnitudes lying in the neighbourhood of the maximal limit of safety are employed, accord well with our general experience of electrocardiograms, and with our knowledge of the rapidity with which their summits and depressions are inscribed. The most important feature is the occasional abolition of S in lead II and in lead III; the remaining changes are insignificant and almost negligible.

It is evident that within certain limits different deflection times are suitable for individual subjects and individual leads, and it is also evident that a given deflection time may affect one curve in one way, another curve in another way. But, speaking of the aggregate, it may be assumed that, if maximal deflection times of between 0.020 sec. and 0.025 sec. are employed, curves obtained from young and normal subjects will be affected only to a trifling extent, and that if the smaller value is adopted any distortion which occurs will be so slight as to be negligible.

THE ELECTROCARDIOGRAMS OF 59 SUBJECTS.

The accompanying tables (Tables III and IV) are arranged in columns which require brief explanation. We have inserted columns for the date of observation, the age of the subject, his height and weight, and the heart rate as calculated from the actual curves. In an end column, under the heading "Remarks," we have inserted a list of infectious diseases from which the subjects of the investigation have suffered.

* In fig. 12 II, S varies from 1 to 2 mm., but the average measurement is about 1 mm.

† These small changes in R are probably largely accidental.

‡ These gains, like many of the losses in R and S , are probably accidental and dependent upon natural and slight variation in the heights of peaks from time to time.

The remaining columns refer to the size of the heart, the character of the heart sounds, and finally to measurements obtained from the curves.

The Size of the Heart.

The size of the heart has been estimated by percussion of its deep limits. We are aware of many possible sources of error in taking the maximal limits of dulness, as measured from the mid-sternal line by percussion.* In taking these subjective readings, the personal factor is an important one, for few people percuss the heart in a precisely similar fashion, or recognise the same limits of dulness in health; the percussion readings have consequently been taken by one of us and have been compared to a standard obtained as a result of his own individual experience in this respect. In accordance with this standard the maximal limits of normal dulness have been arbitrarily fixed at 2.5 inches on the right side and 4.5 inches on the left side, measuring always from the mid-sternal line.

Measurements of Curves.

So far as possible the summits and depressions of the electrocardiographic curves have been measured from a base line, lying at the level of the commencement of the summit *P*. This base is very serviceable for the measurement of *P*, *R*, *S*, *T*, and *U*. *Q*, also, often starts from it; but where, as is sometimes the case, the curve following *P* dips below the horizontal, *Q* starts at this somewhat lower level (fig. 9), and the measurement has then been taken from the point of its commencement.

We have constructed two additional columns, in one of which the *P-R* interval is stated; the *P-R* interval is tabulated for lead *II* only. In the other column the deflection time of the string, for an excursion of 1 cm., and in response to a standard current of $\frac{1}{1000}$ volt, is given. Certain of these last-named values are marked approximate; they are deflection times belonging to curves which were taken in batches, a single deviation time being calculated and checked for a batch of observations.

The asterisks in the table signify that the peak in question was split. In the case of the *P* summit the division into two parts was usually at the apex of the peak. Where *R* or *S* have shown bifurcation the splitting has been in its opening phase, or at its centre.

Where two quantities are given for the height of a *T* summit, two distinct variations have been present, and are represented in the table in the correct order, the signs + (plus) and - (minus) are used to indicate upward and downward variations, respectively.

Where there has been variation in the size of a peak from cycle to cycle, an average reading is given.

* Measurement of the heart in the living subject, whatever the means adopted, has a comparative rather than an actual value.

TABLE

No.	Initials.	Date.	Age.	Height.	Weight.	Heart rate.	Heart limits.		Heart sounds.	Lead I.					
							Right.	Left.		P.	Q.	R.	S.	T.	U.
1	C. E. S.	8.12.11 11.1.12 11.1.12	24	ft. in. 5 6	st. lb. 11 0	82 82 82	1.5	4.25	N.	0.3 0.3 0.3	Tr. 0.5 0.5	3.0 3.0 3.0	0.5 0.5 0.5	2.0 2.5 2.5	0 0 0
2	D. N. S. S.	14.12.11	24	5 11.5	10 5	90	1.5	3.6	N.	0.3	0	3.0	1.5	1.0	Tr.
3	A. C. S. C.	14.12.11 19.1.12	25	5 10	9 0	56 72	2.25	4.0	N.	0.7 0.7	0.5 0.5	3.5 3.5	1.0 1.5	2.0 2.0	Tr. Tr.
4	A. R. McG.	12.12.11	24	5 11	12 0	82	2.25	4.0	N.	0.5	0	3.0	3.0	1.0	Tr.
5	F. C. S.	8.12.11	29	5 8.5	12 0	60	1.25	3.75	Cardio-pulm. murmur.	0.3	0	2.0	1.0	1.5	Tr.
6	C. W. M.	31.10.11	26	5 5.7	8 0	64	1.75	4.0	N.	0.5	0.5	6.0	2.0	2.5	0
7	C. E. A. G.	8.12.11 12.1.12 12.1.12	24	5 11	10 12	82 90 82	2.12	4.0	N.	0.5 0.5 0.5	0.3 0.3 ?	4.0 3.5 3.5	4.0 4.0 4.0	2.0 1.5 1.5	? ? ?
8	J. E. T. J.	14.12.11	24	5 9.5	10 3	72	2.0	3.62	N.	0.3	0	3.0	5.5	-1.0 +0.5	Tr.
9	F. H. R.	20.1.12 22.1.12 23.1.12	22	5 10.5	10 10	69 75 82	2.0	3.6	N.	1.0 1.0 1.0	0 0 0	6.0 5.5 6.0	4.0 4.0 4.0	3.5 3.0 4.0	Tr. Tr. Tr.
10	D. P. P.	5.12.11	25	5 8	8 10	80	2.5	4.5	N.	0.5	Tr.	2.0*	5.0	1.5	Tr.
11	J. M. E.	8.12.11 12.1.12 12.1.12	21	5 11	11 13	56 59 60	1.75	3.75	N.	0.5 0.5 0.5	0 0 0	5.0 5.0 5.0	2.5 2.5 2.5	1.5 1.5 1.5	? ? ?
12	H. C. P.	8.12.11 12.1.12 12.1.12	26	6 3	14 0	90 72 69	2.0	4.25	N.	0.5 0.5 0.5	0 0 0	3.0 2.5 2.5	2.3 2.3 2.3	3.0 3.0 2.5	0 0 0
13	H. W. H.	12.12.11	23	5 10	10 7	75	2.0	3.25	N.	0.5	0.3	3.5	2.5	1.5	Tr.
14	G. G. A.	30.11.11 15.12.11 15.1.12 15.1.12	27	5 8	11 5	62 66 60 72	2.0	3.75	N.	0.7 0.7 0.7 0.7	0 0 0 0	4.5 5.0 4.0 3.5	2.5 3.5 3.0 3.5	3.3 +2.3 -0.5 +2.0 -0.5 +1.3 -0.5	0 0 0 0
15	F. S. F. B.	30.10.11 17.1.12	28	5 11.7	11 0	60 66	2.0	4.25	N.	0.5 0.5	0 0	5.5 5.0	4.0 3.5	2.5 1.5	0 0
16	T. L.	29.9.09 12.1.12	39	5 8.5	10 7	74 90	2.0	4.0	N.	1.0 1.0	0 0	2.0* 1.5*	3.0 3.0	3.0 1.7	Tr. Tr.
17	J. W.	5.12.11	24	5 11.5	10 0	54	1.5	4.25	N.	0.5	0.2	3.5	3.5	4.0	Tr.
18	A. D. E. B.	12.12.11	25	5 8.2	10 0	78	2.0	4.0	N.	0.5	0	4.5	4.0	3.0	0
19	L. L.	4.12.11	23	5 11	10 1	94	1.75	3.5	N.	Tr.	Tr.	2.5	1.0	1.5	0

† α = measles; β = mumps; γ = chicken-pox; δ = whooping cough;

III.

Lead II.						P-R interval.	Lead III.						Deflection time.	Remarks.†
P.	Q.	R.	S.	T.	U.		P.	Q.	R.	S.	T.	U.		
1·0	2·5	12·5	4·0	2·5	Tr.	0·15	0·7	2·5	12·0	3·0	1·0	0	0·023 ap.	α, β, γ.
1·3	2·5	14·0	4·5	2·7	Tr.	0·16	1·0	2·5	13·5	3·0	1·0	0	0·021	
1·3	2·5	15·0	4·5	2·7	Tr.	0·16	1·0	2·5	13·5	3·0	1·0	0	0·016	
1·0	1·0	13·0	3·0	3·0	0·3	0·15	1·0	1·0	10·5	3·0	2·0	Tr.	0·013 ap.	α, γ, δ, rheumatic pains.
1·0*	Tr.	11·0	4·0	5·0	0·8	0·16	0·7*	1·0	8·0	4·0	3·0	0·3	0·013	α, β, ε.
1·0*	Tr.	11·0	4·0	4·5	0·7	0·15	0·7*	1·0	8·0	3·5	2·0	0·3	0·014	
1·0	1·0	13·0	4·0	1·5	Tr.	0·16	0·5	1·0	7·0	1·7	-0·5 +0·5	?	0·013	α, β, γ, δ, η, chronic sore throat.
1·0	0	6·0	3·3	+2·0 -0·5	Tr.	0·13	0·5	0	5·0	2·0	1·0	Tr.	0·023 ap.	α, ζ.
1·7*	1·0	13·0	4·0	3·5	0	0·15	1·5*	1·0	10·0	3·5	1·7	0	0·016 ap.	α, sore throat.
1·0*	0·5	11·0	3·0	2·0	Tr.	0·15	0·7	1·0	9·0	1·3	1·0	Tr.	0·023 ap.	α, γ, δ, pneumonia.
1·0*	0·7	12·0	3·0	2·0	Tr.	0·15	0·7	1·0	11·0	1·3	1·0	Tr.	0·025	
1·0*	0·7	12·0	3·5	2·0	Tr.	0·15	0·7	1·0	12·0	1·3	1·3	Tr.	0·016	
0·7	0·3	8·0	3·0	+1·0 -1·0	Tr.	0·13	0·5	0·5	7·5	2·0	-0·3 +1·0	?	0·013 ap.	α, δ, ε.
1·3	1·0	10·0	2·0	3·0	Tr.	0·13	0·3	1·5	10·0	0	-1·0	0	0·015 ap.	α, γ, δ, ε.
1·7	1·0	10·0	2·0	3·0	Tr.	0·13	0·3	1·5	11·0	0	-0·5 +0·5	0	0·012	
1·3	1·0	11·0	2·0	3·0	Tr.	0·13	0·3	1·5	10·5	0	-1·0 +0·5	0	0·013	
1·0	0·5	7·0	1·0	1·0	Tr.	0·15	1·0	1·5	8·5	0·5	-1·0	?	0·023 ap.	η, bronchitis.
0·7	1·0	12·0	2·0	2·0	?	0·16	0·5	0·5	9·5*	1·0	0·5	?	0·023 ap.	α, appendicitis.
0·7	Tr.	13·0	2·5	2·0	?	0·16	0·5	0·5	10·5*	1·5	0·5	?	0·028	
0·7	Tr.	13·0	2·5	2·0	?	0·16	0·5	0·5	10·5*	1·5	0·5	?	0·018	
1·5*	1·3	12·5	2·0	2·7	Tr.	0·16	1·0	1·3	10·0	1·0	0·5	?	0·023 ap.	α, mother had rheumatic fever, she has rheumatoid arthritis and double mitral disease.
1·5*	1·3	12·5	2·0	3·0	Tr.	0·16	1·0	1·3	10·0	1·0	1·0	?	0·021	
1·5*	1·3	12·0	2·0	3·0 ap.	?	0·16	1·0	1·3	10·0	1·0	1·0	?	0·013	
0·7	1·5	15·0	1·0	2·0	Tr.	0·13	0·3	1·0	10·5	0	0·5	?	0·013 ap.	α, β, δ, ε.
1·0	1·0	13·0	0	4·5	Tr.	0·18	0·7	1·0	10·0	0	0·2	0	0·023 ap.	α, β, γ, septic throat two years ago.
1·3	1·0	14·0	1·0	+3·0 -0·5	0	0·19	0·7	1·0	11·0	0·5	1·3	?	0·012	
1·0	1·0	12·0	0	+3·5 -0·5	Tr.	0·16	0·7	1·0	10·0	0·5	1·5	?	0·022	
1·0	1·0	13·0	1·0	+3·0 -0·5	0	0·18	0·7	1·0	11·0	1·0	1·5	?	0·012	
1·0*	0·3	12·0	0	4·0	Tr.	0·16	0·7*	0·5	9·5	0	1·5	0	0·016 ap.	
1·0*	0·3	12·0	Tr.	3·0	Tr.	0·16	0·7*	0·5	9·5	0	1·5	0	0·011	
1·7	0·5	10·5	3·5	2·5	Tr.	0·15	1·5	1·0	8·5	2·5	1·0	0	0·016 0·016	α, δ, sore throat. First curve taken at Leyden by Prof. Einthoven.
1·7	2·0	16·0	1·5	5·0	Tr.	0·18	1·5	2·0	14·0	0	1·5	Tr.	0·023 ap.	α, γ.
1·5	1·0	13·0	0	2·0	?	0·15	0·5	2·0	12·0	0	1·0	?	0·013 ap.	α (twice).
1·7	1·0	12·0	1·0	2·0	Tr.	0·16	1·5	2·0	9·5	0·5	1·5	Tr.	0·023 ap.	β, ζ.

ε = influenza; ζ = scarlet fever; η = diphtheria; * = split.

TABLE

No.	Initials.	Date.	Age.	Height.	Weight.	Heart rate.	Heart limits.		Heart sounds.	Lead I.					
							Right.	Left.		P.	Q.	R.	S.	T.	U.
20	L. B. T.	8.12.11 9.1.12 9.1.12	29	ft. in. 5 11 5	st. lb. 11 0	106 95 97	2.0	4.2	N.	0.3 0.3 0.3	Tr. Tr. Tr.	2.5 2.5 2.5	2.0 2.0 2.0	1.0 1.5 1.5	Tr. Tr. Tr.
21	P. M. M.	8.12.11 8.1.12	34	5 5.5	9 7	92 108	2.0	3.5	N.	0.5 Tr.	0 0	2.5 2.0	1.5 2.0	2.0 1.0	0 0
22	W. B. G.	8.12.11	22	5 7	9 7	90	2.0	4.5	N.	Tr.	0	2.0	1.5	1.0	0
23	H. N.	11.12.11	28	5 6.2	8 8	72	2.0	3.5	N.	0.5	0	3.5*	0	1.5	Tr.
24	M. D. D. G.	31.10.11 8.1.12 19.1.12 22.1.12	29	5 6.5	9 5	88 109 95 95	2.0	4.5	N.	Tr. Tr. Tr. Tr.	Tr. Tr. Tr. Tr.	6.5 6.0 5.5 5.5	1.0 1.0 1.0 1.5	1.0 1.0 1.0 1.0	Tr. Tr. Tr. Tr.
25	T. H. W. I.	12.12.11	31	5 7	10 0	90	1.5	3.25	N.	Tr.	0.5	4.0	1.5	0.7	0
26	M. B. C.	5.12.11 8.1.12 11.1.12	30	5 4	8 5	106 92 80	2.12	3.5	N.	0.7* 0.5* 0.7*	0.5 1.0 0.5	5.5 6.5 6.0	1.5 1.5 1.5	2.5 2.5 3.0	0 0 0
27	A. P.	8.12.11 9.1.12 9.1.12	25	5 8.7	11 0	75 60 66	2.0	4.0	N.	0.5 0.5 0.5	Tr. Tr. Tr.	4.0 4.0 4.0	Tr. Tr. 1.0	2.0 2.5 2.0	0 Tr. Tr.
28	H. M. D.	31.10.11	32	5 10	10 11	100	1.25	3.5	N.	0.5	0.5	5.0	0.5	1.0	0
29	C. McI.	12.1.12 12.1.12 19.1.12	27	5 11	11 3	86 86 82	2.0	4.0	N.	1.0 1.0 1.0	1.0 1.0 1.0	5.0 4.5 4.5	0.5 0.5 0.5	1.5 1.0 1.5	Tr. Tr. Tr.
30	E. W. G.	14.12.11	21	5 11	10 10	66	2.0	3.75	N.	0.5	0.3	6.0	1.0	1.0	0
31	R. L. H.	14.12.11 17.1.11	22	5 5.5	11 3	75 65	2.0	3.75	N.	0.5 0.5	1.0 1.0	6.5 6.5	2.5 2.5	2.0 2.3	Tr. Tr.
32	R. O. E.	12.12.11	19	5 11.2	9 3	70	2.25	3.75	N.	1.0*	0.3	3.5	2.5	2.0	Tr.
33	R. D. K.	12.12.11	20	5 9.5	10 0 (approx.)	69	1.75	3.25	N.	0.5	1.0	10.5	6.0	2.5	Tr.
34	F. J. C.	14.12.11	33	5 8.5	10 0	82	2.12	3.5	N.	0.5	0	4.5	0.5	1.0	Tr.
35	B. N. N.	12.12.11	23	5 10	11 7	60	2.0	3.5	N.	0.3	1.0	8.5	2.0	2.5	Tr.
36	E. R. M.	5.12.11	19	4 8.5	9 12	72	1.75	3.5	Cardio-pulm. murmur	0.7	1.0	8.0	2.5	2.5	?
37	E. M. C.	8.12.11	25	5 7	10 7	62	1.5	4.5	N. 3rd sound	0.5	0.5	6.0	1.5	2.5	Tr.
38	E. A. G.	5.12.11 8.1.12 9.1.12	24	5 7	10 10	86 102 75	1.75	4.25	N.	0.5 0.5	1.5 1.5	7.0 6.0	0.7 0.7	1.5 1.0	Tr. Tr.
39	M. V.	6.11.11	24	5 5	10 2	82	2.25	4.0	N.	0.7	2.0	12.0	1.0	4.0	Tr.
40	F. B. V.	12.12.11	23	5 3	10 2	54	2.12	3.75	N. 3rd sound	0.7	0.7	12.0	2.5	5.5	0

III—continued.

Lead II.							Lead III.							Deflection time.	Remarks.†
P.	Q.	R.	S.	T.	U.	P-R interval.	P.	Q.	R.	S.	T.	U.			
1.0*	1.5	11.5	0	1.0	Tr.	0.13	1.0*	1.0	10.0	0.5	0.5	Tr.	0.023 ap.	a (twice), δ, ε.	
1.0*	1.5	13.0	0	3.0	Tr.	0.15	1.0*	1.0	10.0	0	1.5	Tr.	0.016		
1.0*	1.5	13.0	1.0	3.0	Tr.	0.15	1.0*	1.0	10.0	0	1.5	Tr.	0.013		
1.0	1.0	9.0	1.0	2.0	Tr.	0.15	1.0	1.0	7.0	0.5	0.5	0	0.023 ap.	Asthma.	
1.0	1.0	9.0	2.0	1.5	Tr.	0.13	1.0	1.0	7.5	1.0	0	?	0.016		
1.5	1.5	10.0	1.0	1.5	Tr.	0.13	1.0	2.0	7.0	Tr.	0.5	?	0.023 ap.	a, γ.	
1.3	1.0	13.5	1.0	3.0	Tr.	0.21	1.0	1.0	12.0	1.0	1.3	Tr.	0.013 ap.	a, η, sore throats.	
1.5*	Tr.	15.0	2.0	2.0	0.5	0.16	1.0*	0	11.0	2.0	1.0	Tr.	0.023 ap.	a, smallpox, dysentery, relapsing fever, malaria.	
1.0*	0.5	13.0	2.0	1.5	0.5	0.15	1.0	1.0	6.0	1.0	Tr.	?	0.016 ap.		
1.5*	0.5	14.0	2.5	2.5	0.5	0.16	1.0*	0.5	11.0	2.0	1.5	Tr.	0.013		
1.5*	0.5	15.5	2.5	2.0	0.5	0.15	1.0*	0	10.0	2.0	1.0	Tr.	0.015		
1.0	2.0	13.0	2.0	+2.0 -0.5	Tr.	0.15	1.0	1.5	8.5	0	1.0	0	0.013 ap.	a, δ, ζ, quinsy, tonsillitis often.	
1.0*	1.0	9.5	0	3.5	Tr.	0.13	1.5*	0.5	5.0	0	1.3	Tr.	0.023 ap.	a, malaria, bronchitis.	
1.0*	1.0	10.0	0	3.5	Tr.	0.13							0.013 ap.		
1.3*	1.0	11.0	0	5.0	Tr.	0.13	1.0*	0.5	6.5	0	1.7	Tr.	0.015		
1.0*	0.7	8.5	0.5	3.0	Tr.	0.16	0.5*	1.5	4.0	0.5	1.0	0	0.023 ap.	a, δ.	
1.0*	0.7	9.5	0.5	3.0	Tr.	0.16	0.5*	1.5	3.5	0	Tr.	?	0.023		
1.0*	1.0	8.5	1.5	2.5	Tr.	0.15	0.5*	1.0	5.0	1.0	0.5	?	0.016		
1.0*	1.0	10.0	0.5	1.0	Tr.	0.13	0.7	0.5	6.5	0.5	0.5	Tr.	0.023 ap.	a, δ, η (twice), sore throats, Vincent's angina eight years ago.	
1.0*	Tr.	9.0	1.0	1.5	Tr.*	0.15	0.7	0	5.0*	1.3	0	0	0.025	γ, t, typhoid.	
1.0*	Tr.	9.0	2.0	1.5	Tr.*	0.15	0.5	0	5.0*	2.0	0	0	0.018		
1.0*	Tr.	10.0	2.0	1.5	Tr.*	0.15	0.5	0	5.5*	2.0	0	0	0.011		
1.0	1.0	14.0	1.5	4.5	0	0.13	0.5	0.3	9.0	2.0	3.0	0	0.013 ap.	a.	
1.0	1.0	11.0	3.5	3.0	Tr.	0.16	1.0	1.0	7.0	1.0	0.5	?	0.013 ap.	a, β, γ, δ.	
1.0	1.0	11.0	3.3	3.5	Tr.	0.16	0.7	0.5	5.0	1.0	0.5	?	0.011		
1.0*	0.5	9.0	3.0	2.7	Tr.	0.16	0.5	1.0	6.0	2.5	0.5	0	0.013 ap.	a.	
1.5	1.0	13.0	4.0	2.0	Tr.	0.16	1.5	0	7.0*	0	-2.0	?	0.013 ap.	a, winter colds, appendicitis.	
1.7*	Tr.	9.5	4.5	2.3	Tr.	0.16	1.0	Tr.	3.0	4.0	1.5	Tr.	0.013 ap.	a, septic cellulitis of arm.	
1.0*	1.0	14.0	3.0	3.0	Tr.	0.16	0.5*	1.0	5.0*	2.0	0.5	Tr.	0.013 ap.	a, β, γ, ε, chronic sore throat.	
1.3	2.0	13.5	4.0	1.5	?	0.15	0.7	1.0	6.0*	1.5	-1.0 +0.5	?	0.023 ap.	a, γ, δ.	
1.0	1.5	16.5	2.0	4.0	0.5	0.16	+0.3	0.5	5.5	0	+0.5 -0.5	?	0.023 ap.	a, γ, δ.	
1.5	1.5	11.0	1.5	2.0	Tr.	0.16	1.5	0.5	2.5	1.0	-0.5	?	0.023 ap.	a, γ, ζ.	
1.5	1.5	11.0	2.5	Tr.	?	0.16	1.5	0.5	2.5	1.5	-0.5 +0.5	?	0.016 ap.		
1.0	1.0	10.0	2.5	1.0	Tr.	0.15							0.016		
1.5*	1.5	12.0	0	2.5	Tr.	0.13	1.0*	+4.0	-1.0		-1.0	0	0.016	a, δ, η, tonsillitis.	
1.0	0	9.5	0.5	3.5	0	0.15	0.3	+6.0	-2.0		-1.5	?	0.013 ap.	a, γ, tonsillitis.	

TABLE

No.	Initials.	Date.	Age.	Height.	Weight.	Heart rate.	Heart limits.		Heart sounds.	Lead I.					
							Right.	Left.		P.	Q.	R.	S.	T.	U.
41	O. M.	31.10.11	33	ft. in. 5 9	st. lb. 11 5	78	2.0	4.5	N.	0.7	1.5	7.7	1.0	2.5	Tr.
		19.1.11				86				0.7	1.5	7.7	2.0	2.5	Tr.
42	H. D.	5.12.11	23	5 9	13 1	106	2.0	4.25	N.	0.5	1.0	7.0	Tr.	2.0	Tr.
		12.1.12				88				0.5	1.0	6.5	1.0	2.0	Tr.
		12.1.12				95				0.5	1.0	6.5	1.0	2.0	Tr.
43	A. K. C.	12.12.11	28	6 0	11 2	90	2.5	4.0	N.	0.5	1.0	4.0	1.0	1.5	Tr.
44	J. B. V.	5.12.11	23	5 4	9 0	78	1.75	4.5	N.	0.5	0.5	8.0	1.5	2.0	0
		21.1.12		approx.	approx.	82				0.5	0.5	5.0	2.5	1.5	0
45	P. H.	12.12.11	19	5 9	11 0	54	2.0	3.5	N. 3rd sound	0.5	1.0	7.0	3.0	+1.0 -0.5	Tr.
46	M. H. B.	30.10.11	18	5 4	8 0	82	1.25	4.0	N.	0.5	1.0	8.0	1.0	2.5	0
47	L. T.	7.12.11	25	5 8	10 9	69	2.0	4.5	N.	0.7	0.5	6.5	1.5	3.0	Tr.
		19.1.12				76				0.5	0.5	6.5	2.0	2.0	Tr.
48	E. B. J.	7.12.11	25	5 7.5	10 3	53	2.5	4.0	N. 3rd sound	0.5	0.5	7.0	2.0	2.5	0
		9.1.12				69				0.5	0.7	9.5	3.0	3.0	Tr.
		9.1.12				75				0.5	0.7	9.5	3.0	3.0	Tr.
49	W. J. M.	5.11.11	27	5 8	10 10	69	2.0	4.25	N.	0.5	0.5	5.5	0	2.0	0
		15.1.12				95				0.5	0.5	6.0	0	1.5	Tr.
50	G. C. C.	30.10.11	35	5 7	9 7	70	1.5	3.5	2nd reduplic. at apex, and pulm.	0.7	1.0	4.5	1.0	2.5	Tr.
		19.1.12				88				0.7	1.0	4.5	1.0	2.0	Tr.
51	R. H. L.	20.12.11	23	5 7	10 0	66	2.0	3.75	N.	0.7	1.0	5.5	1.0	2.3	Tr.
		17.1.12				60				0.7	1.0	5.0	1.0	2.3	Tr.
		17.1.12				76				0.7	1.0	5.5	1.0	2.7	Tr.
52	W. E. K.	12.12.11	23	5 7	10 12	48	2.25	3.75	1st sound redupl.	0.3	0.5	5.5	2.5	3.5	0

Measurements of the Curves of Fifty-two Normal Subjects.

The Summit P.—*P*, the auricular summit, has been constantly found in all instances, and in each lead. It consists in the main of an upward deviation, the limits of which lie between a trace* and 1 mm. in lead *I*, a trace and 1.7 mm. in lead *II*,† a trace and 1.5 mm. in lead *III*.

P has bifurcated at its summit in a number of instances, and this bifurcation must be regarded as a normal feature of many curves, from whichever lead such curve is

* By a trace we wish to express an observed measurement which is less than 0.3 mm.

† This limit is commonly surpassed in clinical cases of mitral stenosis.

III—continued.

Lead II.						P-R inter- val.	Lead III.						Deflection time.	Remarks.†
P.	Q.	R.	S.	T.	U.		P.	Q.	R.	S.	T.	U.		
1.5	0.5	7.5	0.5	2.5	Tr.	0.16	1.0	+2.0	-1.5	-0.5 +1.0	?	0.016 ap.	Nil.	
1.5	0.5	7.0	0.5	2.5	Tr.	0.16	1.0	+2.0	-1.5	-0.5 +1.0	?	0.011		
1.5	0	8.5	2.0	2.5	Tr.	0.16	1.0	+2.5	-2.0	0.5	?	0.023 ap.	α, η.	
1.5	0	8.5	2.0	2.5	Tr.	0.16	1.0	+2.5	-2.0	Tr.	?	0.020		
1.5	0	9.0	2.0	2.5	Tr.	0.16	1.0	+2.5	-2.0	Tr.	?	0.010		
1.7	Tr.	7.5	2.0	1.7	Tr.	0.16	1.5	+2.0	-2.0	1.0	Tr.	0.013 ap.	Smallpox, malaria.	
1.0*	0.3	5.5	2.0	1.0	Tr.	0.13	0.5*	-2.0	+0.5	-1.0	0	0.023 ap.	Malaria.	
1.0*	0.3	4.0	2.0	1.0	Tr.	0.13	0.5*	+2.0	-3.0	Tr.	0	0.014 ap.		
0.7	Tr.	8.0	1.0*	+1.0 -0.5	0	0.15	Tr.	+3.0	-2.0	Tr.	?	0.013 ap.	α, ε, typhoid, jaundice.	
1.5	Tr.	8.2*	2.0*	1.5	Tr.	0.17	1.0	+2.0	-2.0	-0.7	0	0.016	Furunculosis (recently).	
1.5*	0	10.5	2.0	+4.0 -0.5	Tr.	0.15	0.5	+2.0	-1.0	1.0	0	0.023 ap.	α, β, γ.	
1.0*	0	8.0	2.0	+3.0 -0.5	Tr.	0.15	Tr.	+1.0	-2.0	Tr.	0	0.011		
Tr.	1.0	10.0	1.0	2.5	0	0.2	Tr.	+2.5	-1.5	-1.0	?	0.023 ap.	α, β, ε.	
1.0	1.0	9.0	1.5	2.0	Tr.	0.2	Tr.	+3.0	-3.5	-1.5	?	0.021		
0.7	0.5	8.5	2.0	2.0	Tr.	0.2	Tr.	+2.0	-2.5	-1.5	?	0.013		
0.7	0	5.0	2.5	2.0	0.7	0.15	0.7	+2.0	-3.0	Tr.	0	0.023 ap.	α, γ, bronchopneumonia.	
0.7	0	5.0	2.5	2.0	0.5	0.15	0.5	+2.0	-4.5	Tr.	0	0.013		
1.5	0.5	6.7	2.0	4.0	Tr.	0.16	1.3	+4.0	-1.0	2.5	0	0.016 ap.	δ.	
1.5	0.5	7.0	2.0	3.0	Tr.	0.16	1.3	+4.0	-1.0	2.0	0	0.013		
1.3	0	7.0	4.0	2.5	Tr.	0.13	1.0	0	2.0*	3.5	Tr.	0	0.020	α, η, sore throats often.
1.0	0	7.0	3.5	2.0	Tr.	0.13	1.0	0	2.0*	3.0	-1.0	0	0.020	
1.3	0	7.0	4.0	2.5	Tr.	0.13	1.0	0	2.0*	4.0	-1.0	0	0.016	
1.0	0	7.0	3.5	4.0	0	0.16	0.3	1.0	2.0	3.5	0.5	0	0.013 ap.	α (twice), γ, tonsillitis.

taken.* It has been found twice in lead I, 17 times in lead II (figs. 2, 8, and 16 III), and 10 times in lead III.

Splitting in lead I or in lead II has never been observed except in conjunction with splitting in lead II.

The Depression Q.—Q, the first ventricular variation, was found in 37 instances in lead I, in 45 instances in lead II, and in 36 instances in lead III (the 12 instances in which Q, R, and S are bracketed are excluded; Q³ was present, therefore, in 36 out of 40 instances). The limits of measurement in lead I varied from 0 mm. to

* Bifurcation of P has been commonly regarded as a sign associated with hypertrophy of the auricular portion of the heart. This footnote and those which succeed it, and refer to clinical findings, are given as explanatory of the general purpose of our observations rather than as statements of fact.

2.0 mm., in lead *II* from 0 mm. to 2.5 mm., in lead *III* from 0 mm. to 2.5 mm. (the last limit is 4.5 if the downward deflections of the bracketed curves are included).

The Summit R.—*R* has been present in all instances and in all leads. The limits of its variation have been from 1.5 mm.* to 12 mm.† in lead *I*, from 4 mm. to 16.5 mm. in lead *II*, and from 2 mm.‡ to 14 mm.§ in lead *III*.

Splitting of *R* is comparatively rare; it has been seen in lead *I* in three instances; in lead *II* in one instance; in lead *III* it has been present in six instances (fig. 4), in which the question of its identification was not complicated.¶ In 11 other instances, of which we shall speak more fully, *R* might also be considered split; these are the cases in which, in lead *III*, a number of small upward and downward variations open the ventricular systole (so-called splintering; see fig. 3). Such curves are bracketed in Table III and are found together, namely, Nos. 39–50.

The Depression S.—*S* has been found in 50 instances in lead *I*, in 49 instances in lead *II*, and in 31 instances in lead *III* (the 12 instances in which *Q*, *R*, *S* are bracketed are excluded; *S*³ was present, therefore, in 31 out of 40 instances). The limits of *S* in lead *I* have been 0.6 mm.,§ in lead *II* 0.4–5 mm., in lead *III* 0.4 mm.** (the last limit becomes 4.5 if the downward deflections of the bracketed curves are included). Splitting of *S* has never occurred in lead *I*; it has been present in two instances in lead *II*. Apart from the 11 cases of splintering in the opening events of ventricular systole, a division of *S* has not been seen in lead *III*.

The Summit T.—Some trace of *T* has been present in all subjects and in all leads. As a rule, it takes the form of the generally recognised variation, a gradual rise and a steeper fall. Its limits in lead *I* have varied from 0.5 to 5.5 mm. Lead *I* has never shown complete inversion, that, is to say, *T* has never been a purely downward deflection in this lead. But it has shown partial inversion in one instance, a small downward deflection being succeeded by a small upward one. In lead *II* the maximal upward deflection of *T* has reached 5 mm., the minimal being no more than a trace. Complete†† or partial inversion in lead *II* has not been seen. In lead *III* the maximal deflection has been 3 mm. Complete inversion (figs. 4, 5, 7, and 15, *III*)

* This limit is commonly passed and *R*¹ is uniformly small in clinical cases in which, as in mitral stenosis, there is reason to believe right-sided hypertrophy of the heart is present.

† *R*¹ appears to be uniformly tall when there is clinical evidence of left-sided hypertrophy.

‡ This limit becomes 0.5 if the bracketed curves are included. *R*³ is generally of small amplitude when there is evidence of left-sided hypertrophy.

§ *R*² is generally tall when there is evidence of right-sided hypertrophy.

¶ Splitting of *R* is not at all uncommon in pathological cases, though its significance is at present unknown.

‡ The last limit is commonly surpassed in clinical cases in which there is evidence of right-sided hypertrophy.

** This limit is commonly surpassed, and *S*² appears to be uniformly deep in clinical cases where there is considerable hypertrophy of the left ventricle.

†† Complete inversion of *T*² is commonly manifested by pathological hearts, and such inversion is regarded as a sign of value in prognosis.

has been seen in eight instances, the greatest extent of the downward deflection being 2 mm. Partial inversion occurred in six additional instances. Complete inversion of *T* must consequently be considered a rare or abnormal event in all leads except *III*, and in this it is usually associated with splintering of the curve in its opening ventricular events (Nos. 39-50).

The Summit U.—The summit *U*, for which we have arranged a column in Table III, was first described by EINTHOVEN in 1906,* and an illustration of it was given in fig. 23 of his paper. In the particular instance referred to, the amplitude of *U* was well-nigh 1 mm., the largest excursion so far recorded.

U has been seen in a large percentage of the 52 normal electrocardiograms examined. It has been definitely present, in one form or another, in 32 cases (out of 49) in lead *I*, in 44 cases (out of 49) in lead *II*, and in 14 (out of 30) cases in lead *III*. The summit varies very much, both in size and form, from subject to subject. It is seen most prominently in lead *II*, and here its maximal limit has reached 0.8 mm. in our series. If fig. 8 be examined, the wave in question will be seen following directly upon *T*; its approximate duration is 0.16 sec., and it is followed by a long horizontal line, which occupies diastole.

In such a curve as that shown, the variation is upwards; here, as in EINTHOVEN's original curve, *T* fails to reach the base line, running as it does into *U*. Thus the down stroke of *U* is of greater amplitude than the up stroke. Such prominent *U* variations are found as accompaniments of slow heart rates, and are especially prominent where *T* is of considerable amplitude. *U* variations of this magnitude are comparatively rare, but waves of smaller amplitude are extremely common. A slight bowing of the whole line which joins the end of *T* and the beginning of the succeeding *P* is seen in figs. 9, 15, *II*, and 16, *II*. A similar bowing, though less sustained, is seen in fig. 14, *II*. But the curves, in which this bowing occurs, show all the transitions to another type of deflection, which is seen in fig. 12, *II*, and this transition occurs not only from subject to subject, but in the same subject from time to time (figs. 12 and 14). The type of curve to which we refer, and which stands at the one end of the transition, is illustrated by fig. 12, *II*; it may be read as a small, downwardly directed deflection, following directly upon the *T* summit. It is seen even more prominently in lead *I* of the same figure.

KRATZ and NICOLAI, in their recent publication,† have referred to a depression in this situation and, according to their nomenclature, it is termed *F₁*. Especial reference is made to the downwardly directed form, and the transitions between it and the upwardly directed *U*, because, when there is slight shifting of the electrocardiogram as a whole, so that the horizontal line of the pause does not run quite parallel to the millimetre abscissæ, it is often difficult to give accurate numerical expression to this portion of the curve in such a table as we now publish. Where

* "Le Télécardiogramme," 'Archives Internationales de Physiologie,' 1906, vol. 4, p. 149.

† 'Das Elektrokardiogramme,' Leipzig, 1910.

the depression is definite, we have included it in the column for the T variation as a minus quantity. It must be clearly distinguished in such a table from partial inversion of T , such as is seen in fig. 3, and such as is expressed in our table by a minus quantity followed by a plus quantity.

So far as we are aware, no attempt has been made to settle the relation of the U variation to the end of ventricular systole. Where it consists of a slight bending of the whole line joining the termination of T and commencement of the succeeding P (figs. 9, 15, 11 and 16, 11), the estimate is unnecessary. But it becomes essential* where U is a prominent variation limited to late systole or early diastole, as in fig. 8; and this is especially the case since EINTHOVEN, in his original description of it, concluded that it belongs to systole.

We have consequently used the instances in which it was most prominent in our series for this purpose, taking simultaneous electrocardiographic and carotid curves. The U variation in fig. 17 has an approximate duration of 0.16 sec. The bottom of the dirotic notch d is marked upon the carotid curve, and an interval of 0.03 sec. is allowed for transmission delay in the recording instrument (see fig. 18), a further interval of 0.03 sec. is allowed for transmission delay from aorta to carotid,† and the corresponding point is fixed in the electrocardiogram. The curve shows that the variation U lies almost entirely subsequent to semilunar closure. The semilunar closure is estimated as falling a fraction of a second after the downstroke of T . The second sound has been estimated by КАХХ‡ as occurring 0.03 sec. after the downstroke of T . In our own curves the interval is somewhat smaller, but the difference is unessential. U , as a prominent variation, must be regarded, therefore, as almost, if not entirely, a diastolic event.

The Average Amplitudes of the Summits and Depressions.

In estimating the average amplitude of the summits and depressions in the table, we have used those curves which correspond to the smallest deflection time, and have omitted all the tabulated measurements where the deflection time has exceeded 0.018 sec. In all but one instance the deflection times have been as low as 0.016 sec. The calculated values are consequently based upon the curves of 44 subjects. Where a "trace" is tabulated as the value of a summit, we have taken the value at 0.15 mm. In the instance of splintering we have allowed the

* The variation U occurs in the electrocardiograms of pathological subjects, and a thorough knowledge of its relation to other events of the cycle is desirable, for it may be confounded with additional P summits, a matter of much importance when the presence or absence of heart-block has to be determined.

† The allowance of 0.03 second for the transmission time from heart to carotid is taken from our general knowledge of it in other cases. The possible error is probably not greater than 0.01 second. The full delay from apex to carotid in this instance was measured at 0.08 second, and 0.05 second is the customary allowance for the presphygmie interval.

‡ 'Archiv f. d. ges. Physiol.,' 1910, vol. 133, p. 597.

plus quantity as *R* and the minus quantity as *S*. Estimated in this fashion the value in millimetres, or ten thousandths of a volt, for the summits and depressions of the three leads, are as follows:—

Lead I.						Lead II.						Lead III.					
<i>P.</i>	<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	<i>U.</i>	<i>P.</i>	<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	<i>U.</i>	<i>P.</i>	<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	<i>U.</i>
0.52	0.51	5.16	2.06	1.93	0.10	1.16	0.73	10.32	2.23	2.46	0.16	0.81	0.86	6.61	1.73	0.61	0.06

The estimate shows that the average values of the summits and depressions have the following relation to each other in the separate leads:—

$$\begin{array}{ll}
 P^2 > P^3 > P^1 & S^2 > S^1 > S^3 \\
 Q^3 > Q^2 > Q^1 & T^2 > T^1 > T^3 \\
 R^2 > R^3 > R^1 & U^2 > U^1 > U^3
 \end{array}$$

With the exception of *Q*, which has its greatest average value in lead *III*, the remaining summits and depressions have their greatest values in lead *II*; this fact is an argument in favour of the adoption of lead *II*, when a single lead is alone employed. Three of the deflections, *P*, *Q*, and *R*, have their smallest average values in lead *I*, and three, *S*, *T*, and *U*, in lead *III*.

*The P-R Interval.**—The measurement of *P-R* intervals has been taken in lead *II* only, because *P* is usually most prominent in this lead. The measurements in lead *I* and lead *III* are generally within a hundredth of a second of this measurement, but there may be slight differences from lead to lead. The limits of duration of the *P-R* interval are 0.13 to 0.21 sec.; and these measurements apply to heart rates varying from 48 to 109 per minute. The most frequent measurements are from 0.13 sec. to 0.16 sec. The maximum value, 0.21, occurred on a solitary occasion, and 0.18 and 0.19 are infrequent in incidence. There is little relation between the length of the *P-R* interval and the heart rate in our series; the only noteworthy relations being that measurements exceeding 0.16 sec. do not occur with heart rates exceeding 90, and that when the heart rate exceeds 100, the measurement 0.13 sec. becomes, relatively, much more frequent. A *P-R* interval exceeding 0.16 sec., and accompanying a heart rate of 90 or over, should be considered pathological, and a *P-R* interval exceeding 0.20 sec. should be considered pathological in all but exceptional instances, whatever the heart rate may be.†

* We have preferred the *P-R* interval to the *P-Q* interval, a measurement sometimes adopted, because, although the latter gives perhaps a more accurate reading of any given conduction time, it is not always obtainable. By adopting the *P-R* interval, a uniform standard is obtained. The *P-R* interval is of considerable pathological and clinical importance.

† The final conclusions are based, not only upon the 52 normal subjects, but upon measurements in several hundred additional subjects, normal and abnormal.

Grouping of Electrocardiographic Curves.

In arranging the table of observations, we have attempted to group the electrocardiograms so that curves which are similar lie adjacent to each other in the horizontal columns. The arrangement of the curves in this manner has shown that electrocardiograms from normal subjects may be massed into three chief groups, not sharply defined at their borders, but showing a gradual passage of form from one group to the other. The first group consists of electrocardiograms in which R is small in lead I and is larger in lead III (Nos. 1-25, fig. 15); the third group (Nos. 38-52) is characterised by a relatively conspicuous R in lead I and a small or splintered R in lead III (fig. 16).

The arrangement is of more interest because an increase of R in lead III , with a diminution of R in lead I , is considered evidence of hypertrophy of the right ventricular muscle as opposed to the left; and because an increase in the amplitude of R in lead I , and a diminution of it in lead III , is considered evidence of hypertrophy of the left ventricle as opposed to the right (EINTHOVEN*).

As an extreme example of curves from a normal subject, which approach very closely to those which may be considered as characterising right-sided hypertrophy,† we publish fig. 15. The divergence from the mean which is shown by this particular set of curves is so great that we were for some while undecided whether it should be included in the series or not, and this the more, while a history of bronchitic troubles was obtained. But, eventually, when we could find no other physical sign to arouse suspicion of cardiac abnormality, we determined upon its inclusion. As an instance of what might be regarded as a full expression of right-sided hypertrophy, we may cite No. 59, Table IV, one of our rejected cases; in these curves, S reaches 7 mm. in lead I , and R measures 17 mm. in lead III , while R sinks to 5 mm. in lead I .

At the other end of the series is such a curve as fig. 16, where R is tallest in lead I and short in lead III , while S is deepest in lead III . As an instance of what might be regarded as a fairly full expression of left-sided hypertrophy we may cite No. 58, Table IV, again a rejected subject; in this instance R reaches 15 mm. in lead I , S reaches 9 mm. in lead III , while R in lead III is but 3.5 mm.

Emphasis is laid upon these types of curves, and more especially upon the extreme instances, which we have quoted and figured, because they will be of importance in the ultimate solution of the enquiry as to what extent right- or left-sided cardiac hypertrophy can be identified in electrocardiographic curves.

At an earlier stage a type of electrocardiogram was mentioned, which is seen in lead III , and in which the identification of the electric variations at the opening of

* EINTHOVEN, 'Archiv f. d. ges. Physiol.,' 1908, vol. 122, p. 517; and previous citation.

† It not only resembles them in respect of the small R in lead I and the highest R in lead III , but also in respect of the deep S in lead I .

the ventricular systole is difficult or impossible. The subjects from whom the curves were obtained are tabulated as Nos. 39-50, and examples of the curves are shown in figs. 3, 5, 6, and 7. The detailed form is very varied from subject to subject, though remarkably constant in a given subject from time to time. We have specially considered the type because it must be regarded as a normal form of electrocardiogram, because it is commonly associated with partial or complete inversion of *T*, and, finally, because reference to it is necessary in order that our method of tabulating it should be clear.

In figs. 3, 5, 6, and 7, curves taken from four subjects are shown. In the first of the series, fig. 3, there is splintering, the opening events consisting of two summits and a depression. Fig. 5 shows minute downward, upward and downward deflections. Fig. 6 presents a small upward deflection and a deep depression, which is split. Finally, in fig. 7, the opening events consist of a deep downward deflection followed by an upward deflection of almost similar extent; it is a curious curve, but has been met with on other occasions, though, in the present series, the type has not been repeated. In none of these four curves (figs. 3, 5, 6, and 7) is it possible to apply the usual lettering to the opening phases of ventricular systole. A curve (fig. 4), approaching very closely to the same types, may be said to consist of a split summit *R*, followed by a depression *S*.

The Seven Rejected Subjects.

We have stated that, of 59 students investigated, seven have been rejected; the rejections were made either because of abnormal signs obtained in the ordinary physical examination or, as in one instance, upon the appearance of the electrocardiograms themselves.

It may appear that the number of rejections, which is approximately 12 per cent. of the total number of hearts examined, is excessive; but we think it desirable that the tests should be stringent. When the left heart limit has exceeded 4.5 inches, when there have been occasional premature contractions, when there have been cardiac murmurs, whether mitral systolic or tricuspid systolic, the subjects have not been included in the series; six cases fall into this category. One additional case has been rejected on the appearance of the electrocardiograms alone.

The rejections are tabulated in Table IV. The first two subjects of this table showed electrocardiograms which fall within the limits defined by the 52 subjects of Table III in every respect. One was rejected on account of a systolic tricuspid murmur (No. 53), the other on account of the extension of the left heart limit to 5 inches (No. 54).

Four of the remaining subjects (Nos. 55-58) were primarily rejected on the ordinary physical signs, thus, No. 55 presented an apical systolic murmur. In No. 56 the left heart limit extended to 5.5 inches, and occasional premature beats

No.	Initials.	Date.	Age	Height.		Weight.	Heart rate	Heart limits.		Heart sounds.	Lead I.						
				Right.	Left.			P.	Q.		R.	S.	T.	U.			
				ft.	in.	st.	lb.										
53	J. H. L.	11.12.11	29	5	9.5	11	0	100	2.5	3.75	Systolic tricuspid	1.0	1.5	7.0	3.0	1.5	Tr.
54	G. B. K.	8.12.11	24	5	10	14	0	52	2.0	5.0	N.	1.0	0.5	11.0	0	3.0	0
55	W. B. S.	11.12.11	21	5	10	10	0	78	1.5	3.75	Apical systolic murmur	0.7*	0	5.0	3.5	2.0	Tr.
56	L. A. D.	8.12.11	23	5	9	11	0	68	1.75	5.5	Occasional premature beats	0.3	0	5.0	8.0	3.0	0.5
57	D. P.	5.12.11	23	5	1.5	9	0	76	2.5	5.5	N.	0.5	1.0	9.5	2.0	2.5	0
58	J. B. D.	11.12.11	26	5	5.5	9	4	86	2.0	5.0	Apical systolic murmur	0.5	0.5	15.0	0	1.0	0
59	P. V. E.	8.12.11	25	5	11	11	0	69	2.25	4.25	N.	1.0	0	5.0	6.0	+3.0 -0.5	0
		15.1.12						78				1.0	0	6.0	7.0	+3.0 -0.5	0
		15.1.12						78				1.0	0	5.0	7.0	+3.0 -0.5	0

* α = measles; β = mumps; γ = chicken-pox; δ = whooping cough;

were present. In No. 57 and No. 58 the left limit was excessive, 5.5 and 5 inches respectively, and in the last instance a systolic apical murmur was also present.

It seems to us especially noteworthy that of the six rejected subjects to which we have so far referred four presented electrocardiograms of distinctly divergent types. The features which appear to us unusual in the electrocardiograms are given in the ensuing paragraphs.

No. 55.—While the height of *R* in lead *II* reaches 16.5 mm., that is to say, while it attains the maximal limit reached in the remainder of the series, in lead *III*, *R* slightly exceeds the maximum, being 14.5 mm. In this case we lay stress, not so much upon the attaining of the maximal limit, but upon its attainment in *two distinct leads*.

No. 56.—These curves are exceptional, because the maximal limit is exceeded in four separate respects. In lead *I*, *S* measures 8 mm.; in lead *II*, *P* measures 2 mm. and *S* measures 8 mm.; in lead *III*, *P* measures 2 mm.

No. 57.—The exceptional feature of the curves is the excess of *R* in lead *II*, where it amounts to 20 mm.

No. 58.—The exceptional features consist of an increase of *R* to 15 mm. in lead *I*, and an increase of *S* in lead *III* to 9 mm.

We are left with a single subject (No. 59). In this instance no abnormality could be found from the ordinary physical examination of the heart. But the shape of the electrocardiograms is such that we are disinclined to include them in our series

IV.

Lead II.							<i>P-R</i> inter- val.	Lead III.					Deflection time.	Remarks.†
<i>P.</i>	<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	<i>U.</i>	<i>P.</i>		<i>Q.</i>	<i>R.</i>	<i>S.</i>	<i>T.</i>	<i>U.</i>		
1.5	0.5	16.0	2.0	1.5	-	0.13	0.3	+5.0	-2.0	-1.0	?	0.013 ap.	Sore throats often, tonsils removed two years ago; influenza.	
1.0	0	10.0	1.0	3.0	0	0.16	Tr.	0	2.0* 2.0	-1.0	0	0.023 ap.	Nil.	
1.3*	2.0	16.5	2.5	3.0	0.5	0.16	0.7	2.0	14.5	2.0	2.0	Tr.	0.023 ap.	α , β , γ , appendicitis in September, 1911.
2.0	1.0	11.0	8.0	3.5	Tr.	0.18	2.0	2.0	6.0	3.0	Tr.	?	0.023 ap.	α , γ , muscular rheumatism.
1.0	0	20.0	1.0	2.0	Tr.	0.13	1.0	0	11.0* 0	0.5	?	0.023 ap.	α .	
1.0	0	13.0	3.0	1.7	0	0.13	0.5	0	3.5* 9.0	Tr.	0	0.013	α .	
1.0	1.0	12.5	1.5	3.5	Tr.	0.15						0.023 ap.	α , δ , ϵ , η .	
1.0	1.0	15.0	1.5	3.0	Tr.	0.15	0.5	3.5	17.0	Tr.	0.5	0.023		
1.0	1.0	15.0	2.0	3.5	Tr.	0.15	0.5	3.5	17.0	Tr.	0.5	0.013		

ϵ = influenza; ζ = scarlet fever; η = diphtheria; * split.

of normal curves. The exceptional feature in this case is the tall *R* in lead *III*, where it amounts to 17 mm. The limits are also reached or passed by *S* in lead *I*, the measurement being 6 mm. and 7 mm., and in lead *III* by *Q*, which reaches 3.5 mm.

The Constancy of Electrocardiograms in a Given Individual from Time to Time.

We have repeated the electrocardiographic examination in 26 subjects, sometimes after a few days' interval, sometimes after an interval of a month or more. The comparison of such curves is expressed numerically in Table III (Nos. 1, 3, 7, 9, 11, 12, 14, 15, 16, 20, 21, 24, 26, 27, 29, 31, 38, 41, 42, 44, 47, 48, 49, 50, 51, 59). In 24 subjects we have found quite minor variations in the heights or depths of the several summits or depressions from time to time. A change of more than 1 or 2 mm. in the height of *R*, even when it is of considerable amplitude, is exceptional. The summits and depressions of smaller amplitude vary to little more than a proportional extent, with the exception of *T*, which has shown a greater change in two instances (Nos. 14 and 20). The actual resemblance between such curves is, in reality, but poorly expressed by these measurements. The curves resemble each other most closely in their general outlines, and we offer as an example of such resemblance the accompanying figures (figs. 12 and 13), taken from a single subject, with an interval of 31 days between the sittings.

The longest interval which has elapsed in comparisons of this kind occurred in

No. 16, but applies to lead *I* only. More than two years separate the observations, the first of which was made by Prof. EINTHOVEN with his instrument at Leyden. The comparison of these two curves (figs. 10 and 11) is the more valuable because they form a connecting bridge between series of observations taken with two distinct instruments. The comparison emphasises the accuracy of readings when standardised curves are employed.

Only two of the 26 subjects have shown conspicuous alterations, these are Nos. 24 and 44. In one there was a change in the height of *R* from 11 mm. to 6 mm. and back to 11 mm. in lead *III*. In the other (No. 44) there was a change of *R* in lead *I* from 8 mm. to 5 mm. and further changes in the deflection amplitudes of the bracketed *Q*, *R*, *S* in lead *III*. Considering that the curves as a whole have been taken at different times of the day, with different relations to preceding meals and employment, their relative constancy emphasises the uniformity of the electric discharges of the heart muscle from time to time in a given subject; a conclusion which implies that in any given heart the contraction wave, travelling from sinus to ventricle, follows a beaten track. It also demonstrates the accuracy of the method employed. These findings are in entire agreement with our past experience of pathological cases. Where we deal with patients who are the subjects of chronic heart maladies, the constancy in outline and amplitude of the electrocardiograms, from month to month and year to year, is so striking that no one who has collected a large series of such electrocardiograms can have failed to notice it.

The similarity between the electrocardiograms taken from the same subject on different days is so close, and the variations from subject to subject are so numerous (for it may be said that no two series of curves are ever identical), that a series of three leads from any subject would be sufficient to identify the subject in question amongst a considerable number of his fellows.

Summary and Conclusions.

Our observations appear to us to warrant the following summary and conclusions; the latter are intended to apply to young male adults, and it is hoped they may be of service in identifying curves of a distinctly pathological type:

(1) Distortion of the human electrocardiogram, as a result of slackness of the recording fibre, usually commences to show itself when the calculated deflection time of the string lies between 0.020 and 0.030 sec. Such distortion is but slight quantitatively, but it seems desirable that the smaller value should be recognised as a limit, beyond which it is unwise to proceed.

(2) Bifurcation of the summit *P* is a common event in normal human electrocardiograms and is most frequent in lead *II*.

(3) The depression *Q* is found in the majority of electrocardiograms. It is almost always present in lead *III*.

(4) *R* is always present whatever the lead. Splitting of *R* is occasionally found in

normal curves in lead *I* and in lead *III*. Splintering of the curve during the opening phases of ventricular systole is exceedingly common, though it only occurs in lead *III*.

(5) *S* is almost always present in leads *I* and *II* and usually present in lead *III*; it is generally the first variation to show alteration when the string recording it is too slack. The absence of *S* in a large proportion of a series of curves taken from leads *I* and *II* is an indication that deflection times of too high value have been employed.

(6) *T* is always an upward variation in lead *II*. It may show partial inversion in lead *I* on rare occasions. Partial or complete inversion in lead *III* is relatively common and occurs especially in association with the splintering of curves during the opening phases of ventricular systole.

(7) A variation *U*, which has been described by EINTHOVEN, is present in a large percentage of normal electrocardiograms. It follows the closure of the semilunar valves and stretches into diastole for a variable distance. The whole of the diastolic portion of the curve may be slightly bowed or, on the other hand, a prominent summit may be found in the early part of diastole. It is most prominent and is of most frequent occurrence in lead *II*.

(8) The duration of the normal *P-R* interval, as measured in lead *II*, may vary from 0.13 to 0.21 sec. It usually lies between 0.13 and 0.16 sec. A *P-R* interval which exceeds 0.16 sec. and accompanies heart rates of 90 and over is probably of pathological duration. A *P-R* interval of 0.20 sec. and over is probably of pathological duration in all but exceptional instances, whatever the heart rate may be which it accompanies.

(9) The limits of amplitude for the various peaks and depressions approach the values given in the accompanying table, constructed from our 52 subjects. The values are expressed in tenths of millivolts.

Lead I.							Lead II.						Lead III.					
P.	Q.	R.	S.	T.	U.		P.	Q.	R.	S.	T.	U.	P.	Q.	R.	S.	T.	U.
Min.	Tr.	0	1.5	0	-0.5	0	Tr.	0	4.0	0	Tr.	0	Tr.	0	2.0	0	-2.0	0
Max.	1	2.0	12.0	6.0	5.5	Tr.	1.7	2.5	16.5	4.5	5.0	0.8	1.5	2.5	14.0	4.0	3.0	0.3

(10) The average values of the summits and depressions in 44 subjects, using deflection times of 0.018 sec. or less, are calculated as follows:—

Lead I.						Lead II.						Lead III.					
P.	Q.	R.	S.	T.	U.	P.	Q.	R.	S.	T.	U.	P.	Q.	R.	S.	T.	U.
0.52	0.51	5.16	2.06	1.93	0.10	1.16	0.73	10.32	2.23	2.46	0.16	0.81	0.86	6.61	1.73	0.61	0.06

With the exception of Q , which has its greatest average value in lead III , the remaining summits and depressions have their greatest average value in lead II ; it seems, therefore, that when a single lead is adopted for routine observation, lead II should be employed. Three deflections, P , Q , R , have their smallest average values in lead I , and three, S , T , U , in lead III .

(11) Electrocardiographic curves can be arbitrarily divided into three main groups: the first group, in which R^1 is short and R^3 is high; the second group, in which R^1 and R^3 have fair amplitudes; and a third group, in which R^1 is high, while R^3 is short. These groups are not sharply defined.

(12) In examining a series of 59 subjects, seven were rejected from the normal series for various reasons. Six of these manifested abnormal signs upon the ordinary physical examination, and, of these six, four gave electrocardiographic curves which showed considerable divergence from those of the normal series. We are led from these results to the conclusion that the outline of the electrocardiogram given by individual heart cycles forms a valuable test of the heart's condition, and we consider it probable that when two or more peaks or depressions reach or surpass the limits ascertained in a series of 50 normal subjects, the heart is abnormal.

(13) In normal subjects, standardised curves from the same subject show little or no variation in respect of the amplitude of the summits and depressions, from day to day, from month to month, and from year to year. Yet each subject gives electrocardiograms of distinct forms, and so great is the detailed variation from subject to subject that the recognition of any individual amongst a large number is a matter of no great difficulty from the curves he yields.

DESCRIPTION OF PLATES.

PLATE 19.

Fig. 1, $A-F$. (No. 9.)—A series of six electrocardiograms from lead I , taken from one subject at one sitting. Each strip of curve consists of two heart beats, and the curve yielded by the string, when a resistance equivalent to that of the patient and the leading-off electrodes replaces the patient, and 1 millivolt is thrown into the galvanometric circuit. Each curve consequently has attached to it a record of the string sensitivity, including a record of its deflection time in its excursion of 1 cm. The deflection times are calculated by subtracting the distance $a-b$ from the distance $c-e$. The resultant distance $c-d$ is the time occupied by the two movements of the string. The actual deflection time is one-half of this value. The alterations which occur in the measurements and outline of the cardiogram, when the string has varying tensions, are seen. The time-marker is in $1/30$ sec. throughout this and all the remaining curves, with the exception of fig. 10.

- Fig. 2. (No. 34.)—An electrocardiogram from lead *II*, showing an auricular summit which has a value of 1·7 mm., and which is split at its summit.
- Fig. 3. (No. 41.)—An electrocardiogram from lead *III*, showing splintering at the opening events of ventricular systole and partial inversion of *T*.
- Fig. 4. (No. 51.)—An electrocardiogram from lead *III*, showing splitting of *R* and complete inversion of *T*.
- Figs. 5 and 6. (Nos. 44 and 49.)—Electrocardiograms from lead *III*, showing splintering at the opening events of ventricular systole.
- Fig. 7. (No. 48.)—An electrocardiogram from lead *III*, showing a curious arrangement of the deflections which open ventricular systole, and complete inversion of *T*.
- Fig. 8. (No. 3.)—An electrocardiogram from lead *II*, showing splitting of *P* and a prominent *U* variation. The latter summit has an approximate duration of 0·16 sec.
- Fig. 9. (No. 24.)—An electrocardiogram from lead *II*, showing a *U* variation which consists of a slight bowing of the line which joins the termination of *T* to the commencement of the succeeding *P* summit.
- Figs. 10 and 11. (No. 16.)—Two electrocardiograms from lead *I*, taken with an interval of more than two years between them. Each has been standardised in the same manner. The first was taken by Prof. EINTHOVEN in his laboratory at Leyden; the time-marker in this curve is constituted by the vertical lines, which are separated by time intervals of 0·04 sec.

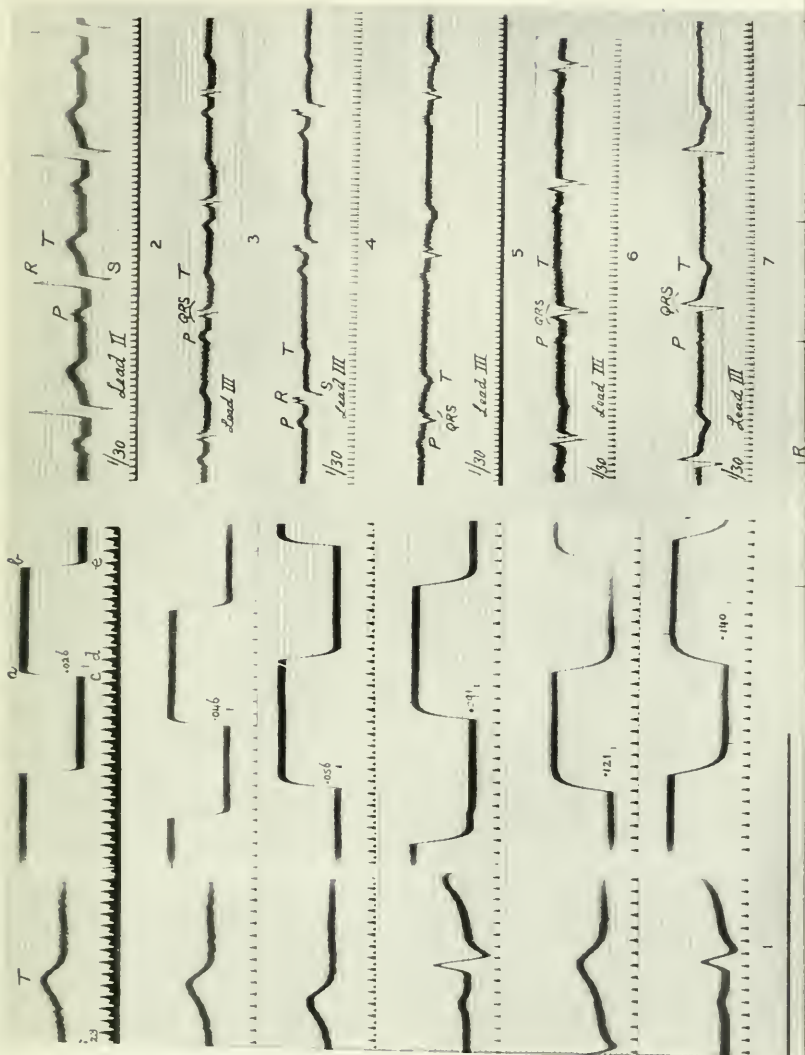
The two curves resemble each other very closely. The chief difference between them is that, in fig. 10, *T* is of somewhat greater amplitude. So far as the remaining summits and depressions are concerned, little difference can be found between them; perhaps *R* is somewhat larger in fig. 10. Both curves show the same exceptional features, namely, a considerable variation in the heights of *R* and *S* from beat to beat. The variation is of similar degree in both curves.

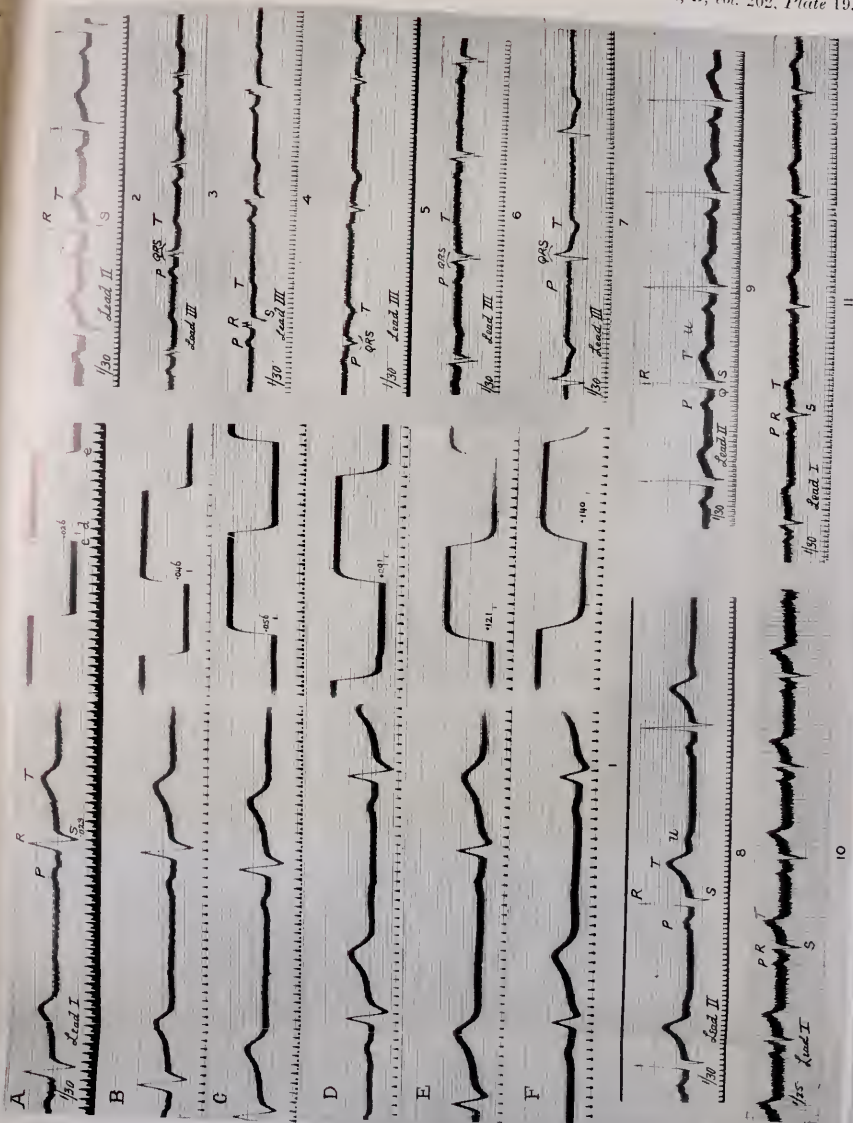
PLATE 20.

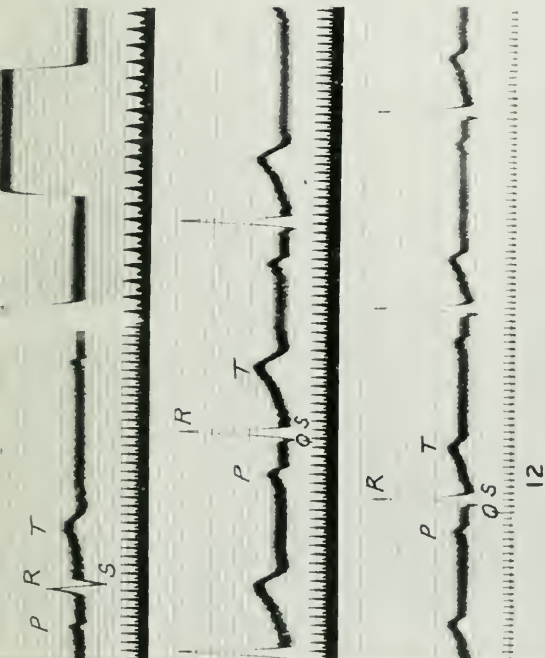
- Figs. 12, 13, and 14. (No. 14.)—Three photographs, each including electrocardiograms from leads *I*, *II*, and *III*, from the same subject. Figs. 12 and 14 were taken on the same day in quick succession. The deflection time for fig. 12 is 0·012 sec., and for fig. 14 it is 0·022 sec. The two series of curves are almost identical; the actual differences between them are mentioned in the text. The chief difference consists in the presence of a small depression *S* in lead *II* in fig. 12. Fig. 13 was taken from the same subject 31 days earlier; it shows, when compared with fig. 12, that the outline and measurements of electrocardiograms are maintained in

a healthy subject from time to time. Figs. 12, 13, and 14 are also published to show variations in the arrangement of the summit *U*.

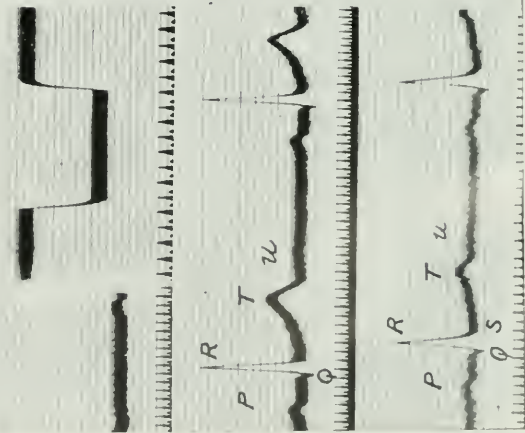
- Fig. 15. (No. 10.)—Electrocardiograms from the three leads of a normal subject, showing a diminution of *R* in lead *I*, a deep *S* in lead *I*, *R* at its tallest in lead *III*, inversion of *T* in lead *III*, and bowing of the diastolic portion of the curve to form a summit *U*.
- Fig. 16. (No. 49.)—Electrocardiograms from the three leads of a normal subject, showing a diminution of the upwardly directed summit at the opening of ventricular systole in lead *III*, *R* at its tallest in lead *I*, a split summit *P* in lead *II*, and bowing of the diastolic portion of the curve to form a summit *U*.
- Fig. 17. (No. 3.)—From the same subject as fig. 8; showing the relation of the summit *U* to the carotid curve. The bottom of the dicrotic notch is marked at *d*. An interval of 0.03 sec. is allowed for transmission of the carotid curve through the recording instrument; a further interval of 0.03 sec. is allowed for the transmission of the arterial wave from aorta to carotid. A vertical line is drawn to the electrocardiogram at the point at which the closure of the semilunar valves is estimated to occur. The summit *U* falls subsequent to this point.
- Fig. 18 is a curve taken to show the delay in transmission in the recording instrument used for the carotid curve of fig. 17. The delay in transmission amounts to 0.03 sec.



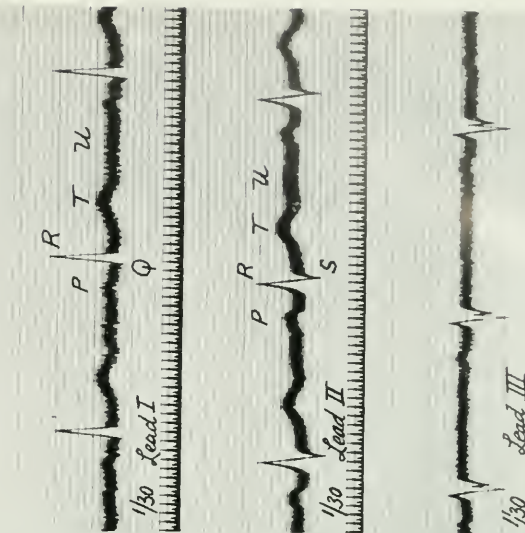


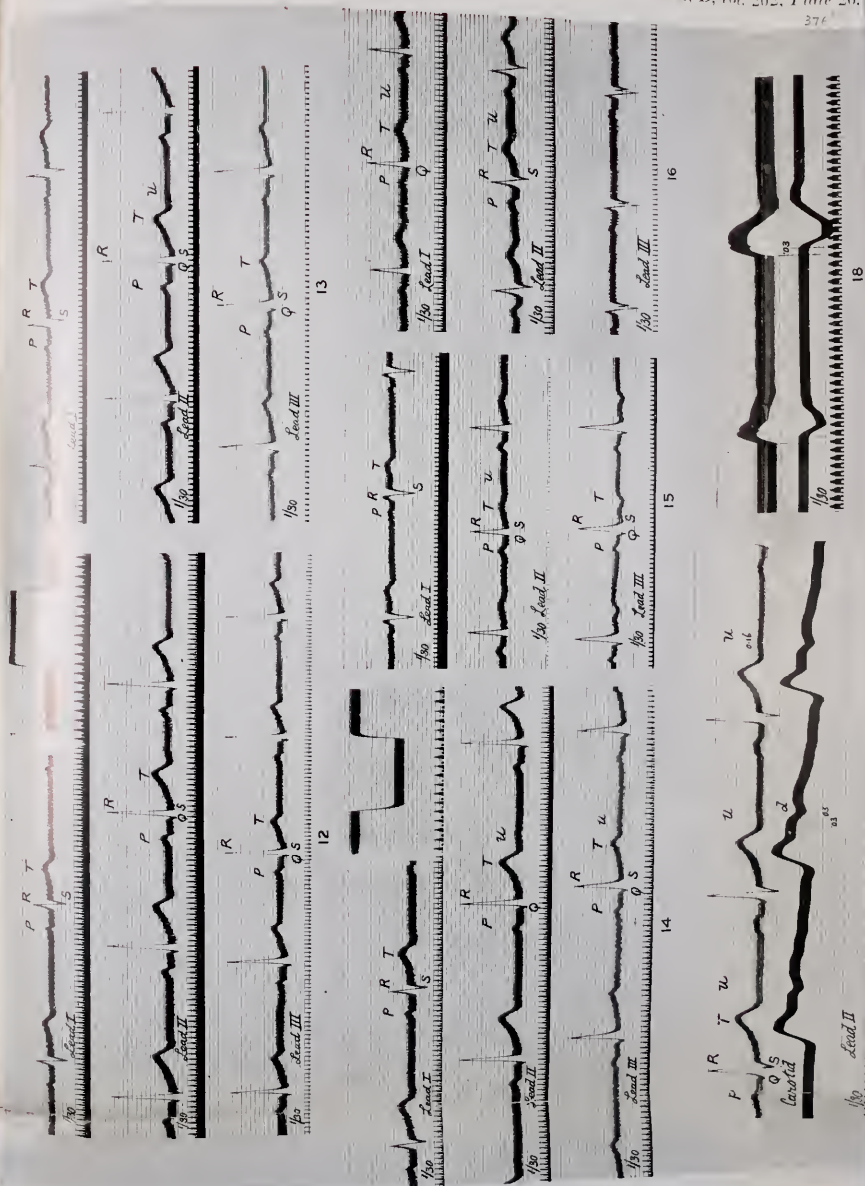


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A NOTE ON BLOOD-PRESSURE READINGS IN CASES OF AURICULAR FIBRILLATION.*

BY

M. D. SILBERBERG, M.D.MELB.,
MELBOURNE, VICTORIA.

IN examining a radial pulse tracing taken from a case of auricular fibrillation one of the most noticeable characteristics is the inequality of the heights of the systolic primary waves—forceful beats and feeble beats occur in no definite order.

This suggests that the systolic arterial blood pressure is also a varying factor in these cases, and that to assign a single value for the blood-pressure readings in such patients is scarcely justifiable.

A simple method for ascertaining the systolic pressure reading for the various beats is as follows: The armlet band of a blood-pressure apparatus is adjusted on one arm—the right is the more convenient. A wrist splint of a Mackenzie ink polygraph is strapped on over the right radial artery, and another over the left radial, and the corresponding wrist tambours are connected by rubber tubing to the receiving tambours of the polygraph. In this way the two radial tracings are recorded on the one strip of paper. The apparatus is adjusted till the best radial impulse in each is obtained, and so that the swings of the writing pens are approximately equal. The paper is allowed to run through, and the pressure in the armlet band is increased by 5 to 10 mm. at a time, and that pressure noted at which the various beats fail to affect the recording apparatus. Sooner or later,

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* From the Cardiographic Department, University College Hospital Medical School.
[175/12]

a complex indicates the origin of the contraction wave, and that such a definite area, known or unknown.

Our observations were made to determine the constancy or inconstancy of

¹ Working under the tenure of a Beit Memorial Research Fellowship in the Cardiographical Department at University College Hospital Medical School.

as the armlet pressure is raised, the smallest beats of the pulse on the corresponding arm are lost. The reading of the manometer at which this occurs gives the minimal systolic pressure. When all the beats are obstructed, the maximal systolic pressure has been obtained. It is found that with highly irregular hearts there may be a difference in the maximal and minimal readings of 60 mm. Hg. With less irregular hearts—that is, those in which the rate is slower—the difference is not so marked, and in those that are only

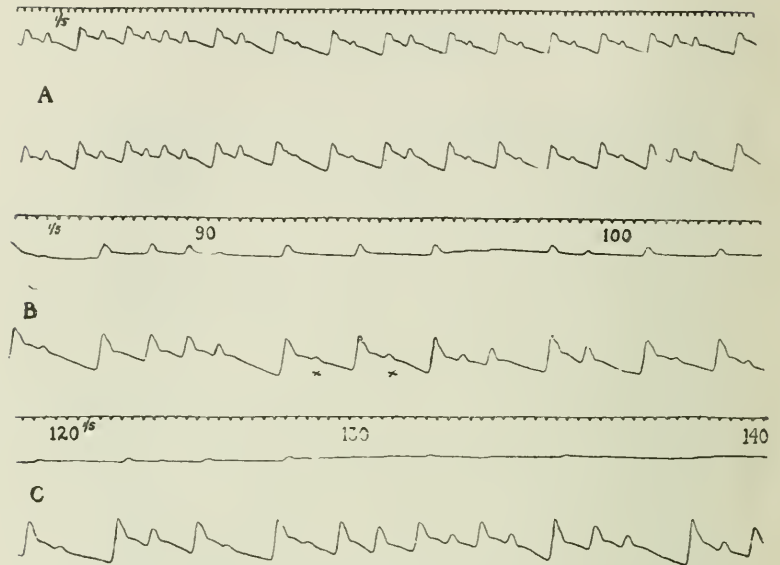


Fig. 1, A, B, and C.—Three strips of tracing (right and left radial) taken from the same patient.

- A. Before brachial compression; all the beats come through.
- B. The smallest beats $\times \times$ disappear at a pressure between 90 and 100 mm. Hg.
- C. The largest beats fail to record at a pressure of 140 mm. Hg.

slightly irregular—as, for example, where the ventricular rate has been markedly retarded by digitalis—the difference may not amount to more than 5 to 10 mm. Hg.

Janeway¹ has previously called attention to the difference in the systolic blood pressure readings in cases of arrhythmia.

The readings taken from 8 patients, all of whom were typical examples of cardiac irregularity due to auricular fibrillation, are given in the following table:

Case.	Blood Pressure Reading of Smallest Beats.	Maximum Blood Pressure Recorded.	Difference in mm. Hg.	Pulse Rate per Minute.
1	150	210	60	56
2	80	100	20	72
3	100	130	30	92
4	95	140	45	74
5	130	140	10	44*
6	115	140	25	84
7	120	140	20	72
8	160	200	40	76

* On digitalis.

This table clearly shows the wide range of blood pressure which an individual case of auricular fibrillation may possess. This variation is of importance, because in the cases in which it occurs single observations of blood pressure, taken in the ordinary manner, possess only a restricted value as an index; the error introduced in continued and comparative observations, where each observation is confined to a reading of the most forcible beats, is also very considerable.

REFERENCE.

¹ T. C. Janeway, *The Clinical Study of Blood Pressure*, p. 205.

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Our observations were made to determine the constancy or inconstancy of

¹ Working under the tenure of a Beit Memorial Research Fellowship in the Cardiographical Department at University College Hospital Medical School.

[Q. J. M., April, 1912.]

THE ORIGIN OF PREMATURE CONTRACTIONS

BY THOMAS LEWIS¹ AND M. D. SILBERBERG

(From University College Hospital Medical School)

With Plates 16 and 17

DURING the systematic examination of patients, the subjects of irregularity of the heart's action, the mechanism in a large number of such patients is found to result from premature contractions arising in one or other heart chamber. Thus the premature beat may arise in auricle or ventricle. The origin of beats in auricle or ventricle may be identified by means of the polygraph, and a wide experience shows that with few exceptions a patient, who exhibits irregularity of the heart, maintains the same type of irregularity from time to time while under observation. The majority of people, who persistently demonstrate premature contractions, are found to have premature auricular or premature ventricular contractions, respectively, and in most cases the types are not mixed in the same case.

Electro-cardiographic examination of the same patients permits a nicer localization of the points of origin of the premature beats. It may be taken as a general rule that the outline of the electro-cardiographic curve, whether it is associated with an auricular or with a ventricular beat, is an index of the direction taken by the contraction wave in the corresponding musculature. It is consequently an index of the points of origin of such contraction waves. Now, premature contractions give rise to electric curves, which, when compared with those of the rhythmic beats, are usually of anomalous form, and the variation in the types, found in conjunction with premature contractions arising in auricle or ventricle respectively, is considerable. The association of the particular anomalous complex with the point of origin of the beat to which it is due is not fully understood; that is to say, the points of origin cannot be accurately located at the present time; but this minute localization does not concern us. We are content to start from the conclusion that in a single patient a given type of electric complex represents a definite course of the contraction wave, and that such a complex indicates the origin of the contraction at a definite point or in a definite area, known or unknown.

Our observations were made to determine the constancy or inconstancy of

¹ Working under the tenure of a Beit Memorial Research Fellowship in the Cardiographical Department at University College Hospital Medical School.

the position of a point or area giving rise to premature contractions in cases examined from day to day, week to week, or year to year.

For if we could show that the type of electric complex accompanying premature contractions in a given case was of fixed form, from time to time, we should have strong presumptive evidence that the site of irritation remained limited for more or less prolonged periods.

We have examined a large number of patients from this point of view and have compared the electro-cardiograms taken on several or many occasions from these cases. For the most part we have adopted one lead, but often we have employed two or three leads and have been able to compare the curves given by such leads on two or more occasions.

Our results are embodied in the following paragraphs, which treat of nine patients. In each instance we have briefly described the type of electric curve obtained and have given the dates upon which the curves were taken and the leads which were adopted. The leads are referred to as *I*, *II*, and *III*; these represent leads from right arm to left arm, right arm to left leg, and left arm to left leg, respectively.

Cases with premature auricular contractions.

Case I. T. M. Premature auricular contractions. The premature beat at each examination showed *P* inverted and of identical form in lead *II*. *P* was constantly iso-electric in lead *I*. The patient was examined on at least seven occasions: 28/8/10, lead *II*; 3/9/10, lead *II*; 8/9/10, leads *I* and *II*; 10/10/10, lead *II*; 1/4/11, lead *II*; 16/6/11, leads *I* and *II*; 18/6/11, leads *I* and *II*; 5/11/11, leads *I* and *II*. Sample curves are shown in Figs. 1 and 2.

Case II. H. B. Premature auricular contractions. The auricular representative of the premature contraction retained a constant form for a given lead throughout all examinations. Lead *I* showed *P* almost iso-electric; lead *II* showed *P* inverted; lead *III* showed a small inverted *P*. The patient was examined on twenty or thirty occasions. We have dated curves as follows: 13/7/9, lead *II*; 28/1/10, lead *II*; 22/4/10, lead *II*; 16/12/10, leads *II* and *III*; 18/3/11, leads *I*, *II*, and *III*; 25/3/11, leads *I*, *II*, and *III*; 30/3/11, leads *I*, *II*, and *III*.

Case III. C. Premature auricular contractions. The auricular representative of the premature contraction was of constant form, it was much smaller than the normal auricular summit, and there was a deeply cut notch at its apex. The patient was examined on the following dates: 2/4/11, lead *II*; 19/5/11, lead *II*.

Cases with premature ventricular contractions.

Case IV. A. M. Premature ventricular contractions. The premature ventricular complexes were of the same general form as those of the rhythmic beats; and this statement applies to the usual three leads adopted. The premature beats probably originated in the *a-v* bundle (*Quart. Journ. of Med.*, 1911, v. 1). Precisely the same pictures were obtained in each separate lead on the several occasions. The patient was examined on the following dates: 2/3/10, lead *II* only; 24/3/11, leads *I*, *II*, and *III*; 19/5/11, leads *I*, *II*, and *III*.

Case V. G. P. Premature ventricular contractions. The premature ventricular complex was of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. Curves were taken from lead *II* on the following dates: 19/11/8, 9/6/9, 3/2/10; leads *I*, *II*, and *III* were used on 17/9/10. On each occasion precisely similar types of premature ventricular complexes were obtained for lead *II*. It is to be noted that the interval between the first and last record extended over a period of nearly two years.

Case VI. L. L. Premature ventricular contractions. In this case the premature ventricular complexes were of the form usually recognized as associated with beats having their origin in the right or basal portion of the ventricular musculature. Curves were taken on 21/9/10, lead *II* only; 8/4/11, leads *I*, *II*, and *III*; 14/6/11, leads *I*, *II*, and *III*. The type of the premature contraction was the same on each of these dates.

Case VII. R. D. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. The patient was examined on two occasions: 26/5/10, leads *I*, *II*, and *III*; 24/3/11, leads *I*, *II*, and *III*. The corresponding leads gave identical pictures on the two occasions.

Case VIII. J. B. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats arising in the right or basal portion of the ventricular musculature. The patient was examined on four occasions: 3/9/10, lead *II*; 29/3/11, leads *I*, *II*, and *III*; 17/5/11, leads *I*, *II*, and *III*; 9/6/11, leads *I*, *II*, and *III*. Corresponding leads gave similar pictures on all occasions. Sample curves are shown in Figs. 3-9.

Case IX. M. F. Premature ventricular contractions. The premature ventricular complexes were of the form usually recognized as associated with beats originating in the left or apical portion of the ventricular musculature. Curves were taken on 12/12/10, lead *II*; 5/4/11, leads *I*, *II*, and *III*; 8/6/11, leads *I*, *II*, and *III*. The corresponding leads gave identical pictures on these three occasions.

Discussion.

We may summarize the results of the examination of these patients. There are three cases in which premature auricular contractions are shown. The electric representatives (*P*) of the premature contractions remain constant in form upon repeated examination. In illustration of this statement we publish Figs. 1 and 2, curves which were taken from Case I. Each figure shows a rhythmic beat (*P*, *R*, and *T*), and following upon the rhythmic beat is a premature beat, which is of similar form to the former, but differs from it in that *P* is inverted. The outline of *P*, the representative of the premature auricular contraction, and a contraction which has taken an abnormal course in the auricle, is the same in the two curves, though Fig. 1 was obtained on August 28, 1910, and Fig. 2 was obtained on June 16, 1911, ten months later. We conclude

that the focus of irritation has remained constant in this patient over the period named.

There are six cases in which premature ventricular contractions are shown. Repeated examination has demonstrated that the electric curves corresponding to the abnormal ventricular beats retain their distinctive outlines in each instance. In illustration of this statement we publish Figs. 3-9, a series of curves taken from Case VIII. Fig. 3 shows two cycles (*P*, *R*, and *T*) belonging to the normal and rhythmic series, and one premature ventricular cycle, which is complicated by the sequential auricular beat (*P*) falling with it. Lead *II* gave this curve, which was taken in September, 1910. Curves, from the same lead and patient, are shown in Figs. 5 and 8; they were taken on March 29, 1911, and May 17, 1911. The pictures are similar; they differ only in small variations in amplitude and as a result of the inconsistency of time-relation between the abnormal ventricular complex and the sequential *P* which falls with it. Thus the abnormal complex in Fig. 5 has, as usual, a bifurcated summit, but the first point of the summit is proportionately higher than in Figs. 3 and 8 because *P* has fallen with it and is superimposed upon it. Fig. 4 is a curve taken from lead *I* on March 29, 1911; Fig. 7 is from the same lead on May 17, 1911. The abnormal ventricular beats are of similar outline. So also in the curves of lead *III*; Fig. 6, taken on March 29, 1911, demonstrates the same type of curve as does Fig. 9, taken on May 17, 1911. We conclude that the focus of irritation, in this instance a ventricular one, has remained constant in this patient.

Precisely similar results have been obtained in each and all of the cases examined, and the same conclusion applies to them; and, as there has been no exception in the series cited and no exception in a number of other cases in which similar observations have been made, we are able to formulate the general conclusion that in patients who exhibit premature contractions, the site of impulse formation, or focus of irritation, tends to be constant from day to day, from week to week, from month to month, and even from year to year.

We believe that this conclusion is of importance, for in many of the patients there has been reason to suspect widespread affection of the musculature, yet each patient has shown but a single and constant focus of irritation. We are led, from this observation alone, to the belief that the focus of irritation has its seat, not in the general musculature, but rather in some specialized tissue or some tissue which reacts to disease in a special manner. For it is difficult to believe, if the site of irritation is the general muscle wall itself, that the irritable focus should be so sharply limited, considering that there is strong presumption that the damage to this muscle is widespread. In coming to this conclusion our thoughts turn naturally to the special tissue which forms the junction between auricle and ventricle. Now the premature contractions seen in the six patients, in whom the focus of irritation lay below the auricle, have been of three types, and three types only. The largest group of cases has shown a type of beat which is recognized as specially associated with the right side of the heart (Figs. 3-9); the second group has exhibited a type of beat specially associated with the left

side of the heart; a third group (a single case, Case IV) has shown a type of beat which almost certainly originated in the junctional tissues, and probably in the main stem of the auriculo-ventricular bundle. Again, the types of curve corresponding to or associated with irritation on the right or left side of the heart are by no means incompatible with the origin of the respective beats in the right and left divisions of the main bundle. The types of curve yielded by impulses travelling along right or left branches alone are known; and, in so far as they are known, they are similar to those which are found in these cases of premature contraction. Moreover, the statements which we have made may be extended to a far larger collection of curves in our possession. With but few exceptions, the types fall into the three groups mentioned; the right type still forms the largest group, the left type forms an almost equally large group, and the third group consists of three similar cases of premature contractions arising in the main stem of the junctional tissues. We can see no evidence opposed to the conclusion in the curves published by other observers, but rather find support in them.

It is true that there are solitary instances which do not conform to the types mentioned: they are rare and isolated, and their occurrence does not invalidate the conclusion to which we lean, namely, that the majority, if not all premature ventricular beats, arise in the special system of junctional tissues.

This conclusion is not new; it was brought forward by Mackenzie in this *Journal* (*Quart. Journ. of Med.*, 1907-8, i. 131) some years ago, and the main evidence which we find in his paper in favour of it is the occasional origin of premature contractions which are localized as arising in the auriculo-ventricular node. It is important that it should not be regarded as in any way a fixed conclusion; we regard it as a point of view which may be held, one which is compatible with our present information, but which still requires the support of far more evidence than we are able to supply at the present time. The conclusion to which we desire to draw special attention is that which emphasizes the constancy of the focus of origin in a single patient from time to time.

Conclusions.

1. The electric curves of premature contractions obtained in repeated examinations of the same patients show a remarkable constancy of outline; this fact is regarded as evidence of the constancy and limitation of the focus of irritation in which they are produced.

2. There are facts which suggest, but do not allow us to conclude finally, that premature ventricular contractions arise as a rule in the special tissues which unite the auricular and ventricular musculature.

DESCRIPTION OF FIGURES.

FIGS. 1 and 2. Two electro-cardiograms from Case I, lead *II*; taken on August 28, 1910, and June 16, 1911, respectively.

FIGS. 3 to 9. Seven electro-cardiograms from Case VIII. Figs. 3, 5, and 8 were taken from lead *II* in September, 1910, and on March 29, 1911, and May 17, 1911, respectively. Figs. 4 and 7 were taken from lead *I* on March 29, 1911, and May 17, respectively. Figs. 6 and 9 were taken from lead *III* on March 29, 1911, and May 17, respectively.



FIG. 1

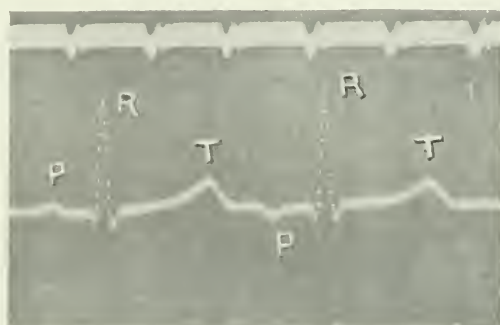


FIG. 2

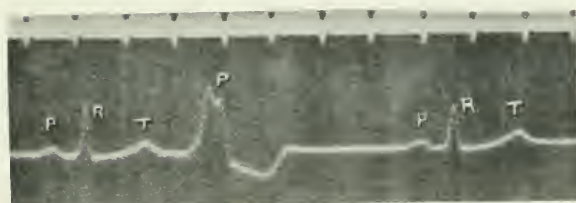


FIG. 3

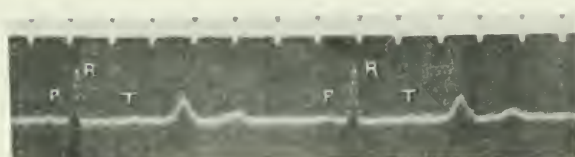


FIG. 4

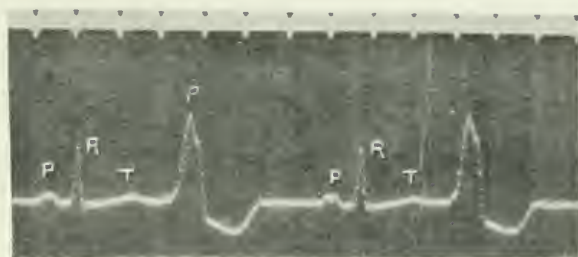


FIG. 5

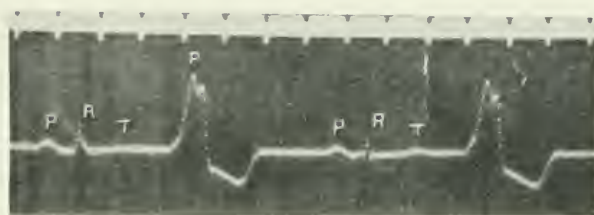


FIG. 6

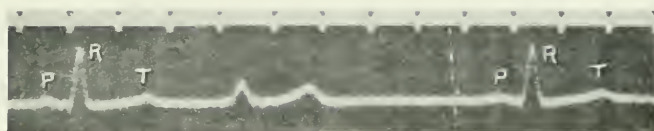


FIG. 7



FIG. 8

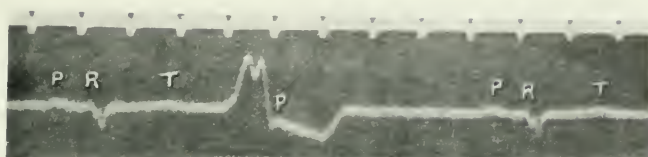


FIG. 9

1003

Ventricular fibrillation caused by stimulation of the cardiac accelerator nerves under chloroform. By A. G. LEVY.

Permanent stoppage of the heart's action through ventricular fibrillation is a consistent sequence of stimulation of the cardiac accelerators on the right side in cats lightly anæsthetised with chloroform. The procedure is as follows:—The right stellate ganglion is isolated by Anderson's method under chloroform. The anæsthetic is carefully regulated and excess avoided. All except the cardiac branches of the

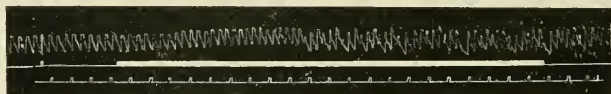


Fig. 1. Time in seconds. Hürtle manometer. Stimulation of left stellate ganglion under 0.5% chloroform. Coil at 100 mm.

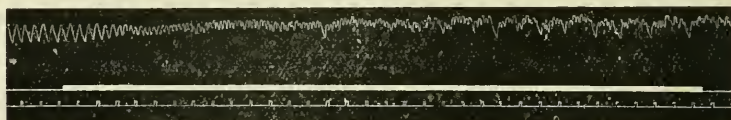


Fig. 2. Ditto. Stimulation of right stellate ganglion under 2% chloroform. Coil at 95 mm.

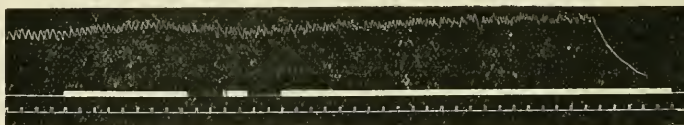


Fig. 3. Ditto. Stimulation of right stellate ganglion under 0.5% chloroform. Coil at 95 mm.

ganglion are divided, and the chloroform having been reduced to 0.5%, the ganglion is stimulated with a faradic current of a strength just too painful to be applied to the tongue. The heart beat at first accelerates and soon passes into an irregular tachycardia which terminates in permanent fibrillation of the ventricles (Fig. 3). The duration of stimulation required to produce this result is variable, seven seconds being the shortest time noted.

Under full anæsthesia induced by 2% chloroform stimulation of the ganglion evokes a similar irregular tachycardia, and even momentary periods of fibrillation may be apparent, but the heart is not brought to a permanent standstill (Fig. 2). These results therefore are related to those already elsewhere¹ described as following the injection of adrenalin under chloroform.

The effect of stimulating the left ganglion is dissimilar. In one case only out of six did I obtain ventricular fibrillation, and in that case the heart was exhibiting spontaneous irregularities when the stimulation was applied. The reaction from the left ganglion is usually far less marked than that from the right; there is less acceleration and the abnormal beats take the form of bigeminæ or of a relatively slow sequence of irregularities (Fig. 1).

¹ Levy, *Proceedings of Physiol. Soc.* Jan. 1911. Levy and Lewis, *Heart*, Vol. III. No. 1.

OBSERVATIONS UPON DISORDERS OF THE HEART'S ACTION.

By THOMAS LEWIS.*

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During the course of a systematic investigation of the heart by means of graphic methods, I have made a number of observations which are not immediately connected with each other. It is my desire, at the present time, to place certain of these observations upon record, and I shall proceed to do so, under distinct headings.

PART I. A SERIES OF CLINICAL CASES.

Section 1. An observation upon ectopic impulse formation.

For the past eighteen months, a lad of eighteen years has been repeatedly examined by means of the electrocardiographic method, because he presented at the first examination, and has continued to show, a hitherto undescribed disorder of the heart's mechanism. He is an engineer's labourer and has always enjoyed excellent health, having suffered from no infectious disease and having been perfectly free from all symptoms of heart affection. The irregularity of his heart's action was discovered during a routine examination by Dr. Marris, to whom he went for the treatment of a bilious attack which resulted from a dietetic indiscretion. The dimensions of the heart are hardly abnormal. The percussion limits lie 1 and 4 inches to the right and left of the mid-sternal line respectively. The sounds are natural. The irregularity has been present constantly from the time when it was first observed until the present day, and its nature, in so far as I shall consider it at the present time, has been unchanging. It consists of disturbances of the sequence which result from the frequent occurrence of premature contractions, and these early contractions arise, as shown by repeated examination, from a fixed and ectopic auricular focus. An example of the irregularity is shown in Fig. 8 (an electrocardiogram from lead II). The ventricular complexes of rhythmic and premature heart beats have a constant and normal form, the auricular complex of the premature beat is inverted. The electrocardiogram shown in this figure is not exceptional, it is an example of the

* Working under the tenure of a Beit Memorial Fellowship. Expenses have been partially defrayed by a grant from the British Medical Association.

pictures, now well-known, which are found when premature auricular contractions are present. The new fact is illustrated in the next figure (Fig. 9), in which electrocardiograms, taken separately from leads *I*, *II* and *III*, are shown. The picture from lead *II* of this figure may be compared with Fig. 1. A premature beat of the usual form is seen towards the end of the curve (Fig. 9 *II*), but in contrast to Fig. 1, the beat which follows it is abnormal.* It springs from the same focus as does the premature beat, a fact which is evidenced by the similarity of the electric changes. Precisely the same phenomenon is seen in the two other leads (leads *I* and *III*) of the same figure. In lead *I* the auricular representative is almost iso-electric, both in the premature beat and in that which follows it. In lead *III* it is inverted in both beats.

What is the nature of the second abnormal beat? Is it of precisely the same nature as the premature beat which it follows; or is it comparable to the beats of the normal type? The answers to these questions are perhaps uncertain, but the evidence is chiefly in favour of the second view. That it belongs to the same order of pathological or *heterogenetic* contractions, as I have termed them, to which premature beats belong, is improbable. When a pair of premature beats occur, they follow each other closely, and I have curves from the same patient in which there is but a very short gap between the separate beats of such a couple. In the present figures, the pause between them is always long. On no occasion have pauses of intermediate length been seen; the pause is generally equal to or falls only slightly short of that which follows an isolated abnormal contraction, and is usually larger than the pauses separating beats of the regular rhythm in the same patient.† It is consequently probable that the second abnormal contraction has arisen by processes similar to those which create the normal beats; processes which are physiological or *homogenetic*.

The occasional slight prematurity of the second ectopic beat, and its site of origin, may be explained by supposing that the discharge of the first or true premature beat hastens physiological impulse formation at the focus in which it arises, and that the new focus, stimulated in the manner suggested, wins in its race with the pacemaker to produce the next physiological impulse. Such a view is supported by other observations. On several occasions I have observed that if the auricle of an animal is stimulated by means of an interrupted current so that a regular tachycardia, or succession of responses, is produced at a faster rate than that of the normal rhythm, the first beat of the escaping auricle, when stimulation ceases, comes, not from the pacemaker, but from the point originally stimulated.

* The occurrence of the abnormal beat has been as common as that of the normal beat, and both have been extremely frequent.

† The analysis is complicated by the occurrence of the slow but accelerating heart rate which succeeds each interruption.

Section 2. An instance of premature auricular contractions, followed by pauses considerably shorter than those separating the regular heart-beats in the same case.

A man of 64 years, who gave a history of rheumatic fever at the age of 24, and who has physical signs of extensive fibroid change in the left lung, was sent to me because he had an irregular heart action.

Apart from the irregularity, there were but few physical signs. The limits of the heart's dulness were normal, and there were no symptoms which could be directly referred to the heart. A systolic murmur at the apex was alone detected.

Several strips of curve, taken from the radial artery, are shown in Fig. 1. Premature beats occur from time to time in the curves. In no instance is the pause following a premature beat compensatory; in most instances it not only fails to be compensatory, but it is considerably shorter than the pause separating the beats of the regular rhythm, which comes before and after the disturbance.

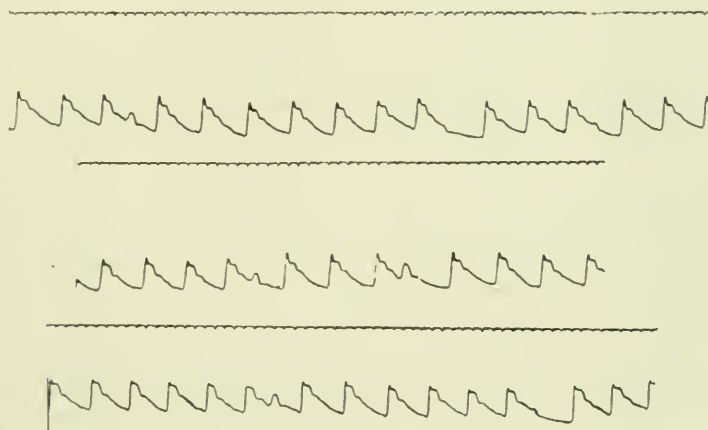


Fig. 1. Radial pulse curves from a patient who showed premature auricular contractions. The pause following a premature beat is usually considerably shorter than the pause separating rhythmic beats. The time marker is in one-fifth seconds in this and all polygraphic curves.

The corresponding electrocardiograms, taken at the same time, are shown in Fig. 10*a* and *b*. Satisfactory curves were obtained from lead *II* only; those from leads *I* and *III* being too tremulous to be of value. Altogether, three premature beats are seen. All arise in the auricle; and, judging from this lead alone, they arise in close proximity to the pacemaker, for the auricular complexes, corresponding to rhythmic and premature beats, seem identical in outline. One of the premature beats is followed by a long pause, but the two remaining ones are succeeded by pauses, which are shorter than the pauses separating rhythmic beats.

It is known that electrical excitation of the auricle, in the neighbourhood of the great veins, produces premature beats which are followed by short pauses ; but pauses which are shorter than those separating rhythmic beats have not been seen previously. Presumably they are due to the presence of a somewhat rare phenomenon, namely, stimulation of physiological impulse formation at the point at which they arise, so that the succeeding physiological impulse is formed more rapidly than usual.

Section 3. In a patient who presented a paroxysm of regular tachycardia, auricular fibrillation developed, and quick changes from one condition to the other were recorded. The same patient demonstrated a regular and exceptionally rapid action of the ventricle while the auricle continued to fibrillate. Curves were obtained within 24 hours of death.

The patient, an unmarried girl of 17 years, was admitted to University College Hospital on November the 9th, 1911, and presented evident symptoms and signs of heart failure.

Her heart was said to have been affected for 7 years ; at the age of 10 she lay in a bed at Gt. Ormond Street Hospital, suffering from swelling and pain of the joints. Her symptoms, shortness of breath, palpitation, weakness, cough and sleeplessness had been conspicuous for 11 weeks prior to her admission.

Cyanosis, orthopnœa and a slight degree of conjunctival jaundice were noted at her entrance into hospital. Ascites, some œdema of the legs, fullness of the veins and enlargement of the liver were present. Crepitations were audible at the bases of both lungs.

The heart's impulse was visible in the third to sixth interspaces ; the limits of dulness lay 1 and 6 inches to right and left of the mid-sternal line as she lay in bed. Systolic and diastolic thrills were present at the apex, and at the same point corresponding murmurs, the last of a grinding character, were audible. The first sound was accentuated, and seemed to fill the whole of diastole ; the ventricular rate was 168 per minute, the heart's action being perfectly regular.

The patient was placed upon digitalis on the 9th ; it was administered in doses equivalent to a drachm and a half of the tincture a day. On the 10th this dose was reduced to an equivalent of 40 minims a day and this was continued until the 17th. She vomited on the last two days of its administration.

I saw her on the 12th, when her pulse was stated to have first become irregular. When examined, a regular tachycardia was found, which was uninfluenced by posture and the rate of which was 153 to 155, but in a few minutes the heart became irregular for a brief period, returning to its former state. This was repeated very many times and the action

of the heart is illustrated by Fig. 2 and 3. In Fig. 2 a period of regular tachycardia, accompanied by the ventricular form of venous pulse, passes into an irregular period also accompanied by the ventricular form of venous pulse. In Fig. 3, a short irregular period is interposed between two regular

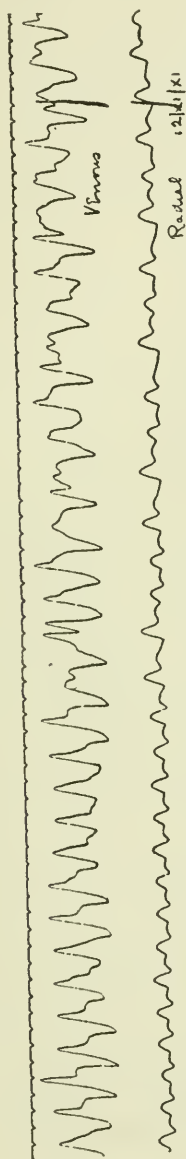


Fig. 2. A polygraphic curve showing the passage of a period of regular tachycardia into an irregular tachycardia. The venous pulse is of the ventricular form throughout. Where a long pause occurs, prominent stasis waves are also present. The mechanism in Fig. 2 and 3 is of the same nature; the figures show the passage of regular tachycardia of auricular origin into auricular fibrillation. The electrocardiogram corresponding to the regular period is shown in Fig. 11.

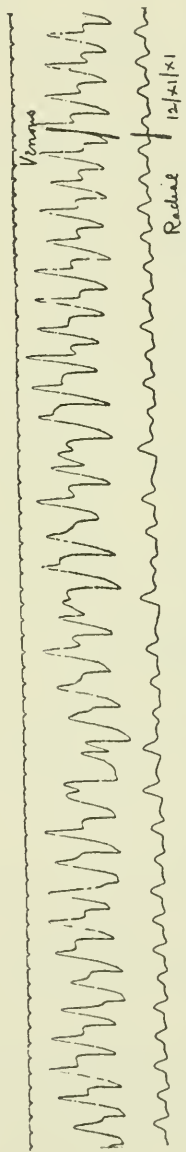


Fig. 3. A polygraphic curve which opens with a paroxysm of regular tachycardia, the rate of which is approximately 150 per minute. The venous curve is of the ventricular form. The regular paroxysm ends and gives place to a period of irregularity of about 5 seconds duration. Then the regular tachycardia is resumed. The period of irregular tachycardia is also accompanied by the ventricular form of venous pulse.

periods. The change from one action to the other continued at short intervals for an hour, and there is little reason to doubt from these curves and subsequent observations that the changes were from regular paroxysms

arising in the auricle to auricular fibrillation. Directly after the polygraphic curves had been secured, the patient was examined electrocardiographically, but by this time a regular paroxysm had become continuous. The curves are shown in Fig. 11. The heart rate is 156 per minute. In lead *I*, *R* is small, *S* is large. In lead *III*, *R* is exaggerated; these are signs which are found almost constantly when the right ventricle is hypertrophied and mitral stenosis is present. The auricular representative is seen in each lead, and it appears to fall a little before the termination of the preceding systole of the ventricle; it is not of the form which usually accompanies mitral stenosis, and arguing from this fact and from the general character of the paroxysm, I am led to the conclusion that the paroxysm was of ectopic auricular origin.

On the 17th the pulse became slow, regular and palpably dicrotic. A mid-diastolic murmur was present; the ventricular form of venous pulse was maintained. The condition of the patient had improved remarkably; the cyanosis, dropsy and orthopnoea had vanished, engorgement was less, the liver was barely palpable; a little ascites remained. Improvement continued, the pulse remaining regular at a rate of 80 beats per minute. On the 18th the digitalis was continued in small doses; 9 minims a day were given until the end. On the 18th and until the 23rd the pulse was regular, the rate varying between 80 and 90. Electrocardiographic curves taken on the 22nd showed a perfectly regular ventricular action at a rate of 90 per minute. They are shown in Fig. 12. The ventricular complexes are of similar general form to those of Fig. 11, though the excursions of the string have decreased and *T* is no longer completely inverted in leads *II* and *III*. There is no sign of co-ordinate auricular contraction, but *P* is replaced by the characteristic oscillations of a fibrillating auricle. That the oscillations arose in the auricle is evident from the special leads taken to demonstrate it. Fig. 13 shows three of these leads; electrodes were placed over the right auricle (*I*), the lead showed conspicuous oscillations; leads were taken from the outer end of the third left interspace to the apex (*II*), and from the epigastrium to the apex (*III*); in these two leads only very faint traces of oscillations were detected from time to time. On the 22nd, therefore, the auricles of this patient were fibrillating while the ventricles maintained their regularity at a rate of 90 beats per minute. Now when auricular fibrillation is accompanied by a regular ventricular action it is assumed that no impulses reach the ventricle from the auricle. The ventricle is considered to respond to impulses formed in the junctional tissues, the intrinsic ventricular pacemaker. Such is the assumption in the present case, though the ventricular rate of 90 must be considered quite exceptional; the ventricular rhythm was quite uninfluenced by posture and deep respiration. A similar instance, in which the rate of the ventricle was 70, has been spoken of by Mackenzie,¹⁰ a case which I examined electrocardiographically. The findings were the same as those stated for the present patient, with the exception that the ventricular rate was slower. It should be remembered that complete dissociation has been seen in an adult in whom the auricles beat at

138 and the ventricles at 66 per minute.¹⁵ While the intrinsic ventricular rhythm is usually 30 or thereabouts, it may be much faster in these exceptional cases; it is especially fast when heart-block has been induced by the administration of digitalis. The complete obstruction of auricular impulses, which has to be assumed in the present case, is attributed to the digitalis; the patient was under its full influence when the regular pulse appeared. The block continued until the 23rd, at which time the patient was on 9 minims a day on digitalis tincture and had not taken the heavier doses for five days.

On the 24th the pulse was grossly irregular and electrocardiograms gave the characteristic pictures of auricular fibrillation (Fig. 14), the ventricle responding to the fibrillation impulses. The ventricular rate was approximately 84 per minute. A number of the ventricular beats were premature (marked with an asterisk in Fig. 14) and of ventricular origin; the remainder showed conspicuous variation in the amplitude of *R*; *T* was inverted in leads *II* and *III*. During the evening of the same day the patient was comfortable and seemed to continue her improvement. She slept well during the following night and was sleeping, though a little restless, a quarter of an hour before death occurred. At this time the pulse was still irregular, as on the preceding day. Apparently she died in her sleep. The patient in the next bed called the nurse, saying that her neighbour looked pale and that her head was back. The girl was dead.

The case may be summarised in the statements that in a case of mitral stenosis admitted for heart failure, regular paroxysms of tachycardia arising in the auricle alternated with periods of fibrillation, while the patient was under digitalis; that subsequently, while the auricles remained in a state of fibrillation, the ventricles beat regularly at 90 per minute; that the regular action of the ventricle gave place to an irregular action, in which *R* showed conspicuous variation in height, in which *T* was inverted in leads *II* and *III*, and in which premature ventricular beats were scattered; the patient died unexpectedly while the heart continued to beat in this manner.*

Section 4. An account of a patient who came under observation with a heart rate of 150. The auricles were found to be beating at 300 per minute. Upon digitalis the auricle passed into fibrillation and subsequently the normal heart rhythm was resumed. A further and brief account of three similar cases.

W. G., a French polisher, 60 years of age, was admitted to University College Hospital on November the 19th, 1911, complaining of shortness of breath, cough and dropsy. He gave a history of having had periodic attacks

* Instances of unexpected death in heart disease are common and of extreme importance. In a number of patients, upon whom graphic observations have been made and who have died without warning, premature ventricular contractions, with or without auricular fibrillation, have been present. The suggested cause of death is sudden cessation of the circulation as a result of the onset of ventricular fibrillation.

of breathlessness of a distressing and exhausting character for three and a half months. He had a very severe attack in October, 1911, which lasted three days. Previously his health had been good; at 17 he was infected with gonorrhœa; at 23 he was laid up for three weeks with a chest ailment of which he remembers but little. He had had neither rheumatism nor syphilis. Of alcohol he had drunk temperately; he had been a moderate smoker.

Upon his admission the temperature was 98° Fahr., the patient was orthopnoëic and slightly cyanosed; there was a little dropsy in the legs; signs of fluid in the abdomen were present. The diffuse heart apex beat lay in the fifth and sixth interspaces. The right limit of dulness was $1\frac{1}{4}$, and the left 6 inches, from the mid-sternal line. The sounds at the aortic cartilage were normal; at the pulmonary cartilage the second sound was accentuated; at the apex the first sound was accentuated. A systolic murmur was present at the apex. The pulse rate was 150 and did not alter with posture. There seemed to be no arterial thickening; the systolic blood pressure varied from 116 to 120 mm. Hg.. The liver was enlarged. The urine was normal. The subsequent events are related in the ensuing paragraphs.

On November the 25th he was placed upon the fresh infusion of digitalis, three drachms being given four times a day.

On the 26th electrocardiograms were taken; as subsequent events proved, they showed 2 : 1 heart-block, the auricular rate being 293 per minute (Fig. 15). From the time of his admission the pulse rate had continued persistently at 145-150 per minute, and the presumption is that during the whole of this period 2 : 1 block was present. Occasional premature ventricular contractions (*P.B.*) were seen and disturbed an otherwise perfectly regular heart action.

On the 28th the mechanism remained unchanged. The auricular rate, recorded electrocardiographically on this day, was 300 per minute.

On December the 1st the recorded rate of the auricle was 299, the ventricle beating at half this rate and occasionally becoming slower as a result of the presence of 4 : 1 periods (Fig. 16).

On the 2nd the recorded auricular rate was 288; the ventricle beat at 72, except for short periods of the 2 : 1 ratio.

On the 3rd, 4 : 1 block was established, the rate of the auricle being 292.

On the 4th, the 4 : 1 block was maintained, the auricular rate being 288, (Fig. 17). The heart limits were $1\frac{3}{4}$ and 6 inches on either side of the mid-line. Systolic and faint early diastolic murmurs were audible at the apex. The auricular sounds could not be heard. The whole condition of the patient had improved conspicuously; there were no symptoms, the cyanosis, dropsy and liver enlargement had disappeared. Pressure upon the right or left carotid sheath, even when light, produced an almost invariable cessation of ventricular action for several seconds (see Fig. 4, 5 and 18). Cessation of the pulse for six seconds was accompanied by pallor and faintness; though consciousness was never lost. During the whole of the period of

ventricular systole the auricles continued their rapid action as before. On this day the chest was screened but the movements of the auricles were not apparent.

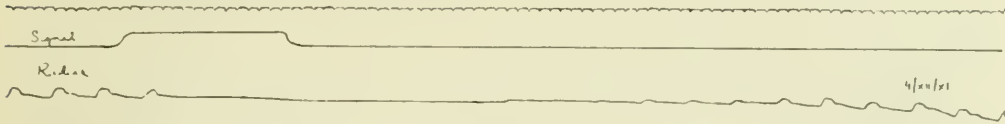


Fig. 4. A radial curve and signal showing the effects of light compression of the right vagus. The vagal compression lasts for a little more than three seconds. Within a second of its onset the pulse disappears and no beat is recorded for a period of approximately 7 seconds. The first radial beat following the pause is weak, and the succeeding beats, which are regularly spaced, show the staircase phenomenon.

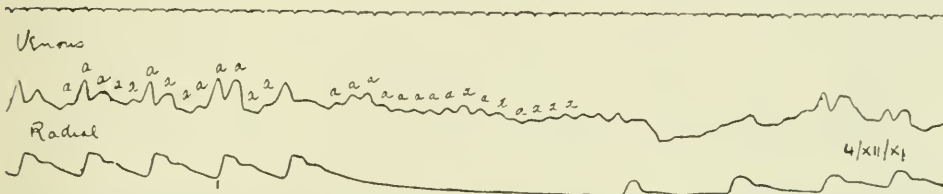


Fig. 5. Venous and radial curves from the same case, showing the effect of left vagal compression. During the opening phase of the curve, 4:1 heart-block is present. The venous curve during this period consists entirely of *a* waves, though it has a superficial resemblance to a normal venous curve, with *a*, *c* and *r* waves occurring as accompaniments of each ventricular heart cycle. When vagal compression produces a higher grade of heart-block, the separate *a* waves become perfectly distinct.

On December the 11th the pulse rate suddenly fell from 72 to 44 and the action of the heart became grossly irregular. Electrocardiograms showed that fibrillation had set in (Fig. 20). The symptomatology was otherwise unaltered.

On the 12th the digitalis was stopped. On the 13th, 14th and 18th polygraphic records showed gross irregularities of the pulse and rates of 45, 56 and 53 respectively.

On the 20th, fibrillation was still present, but the ventricular rate had risen to 62.

A period now intervened during which no observations were made. Upon the 4th of January the heart action was normal and the rate of auricle and ventricle was 63. Electrocardiograms of the restored action, but in which the rate is 90, are shown in Fig. 21; they were taken on the 6th. On both dates premature auricular contraction interrupted the otherwise regular rhythm.

The patient was discharged, much improved in health, on January the 8th.

On the 20th the normal rhythm was still present, interrupted as before by single and successive premature contractions, some generated in the auricle, others in the ventricle. Pressure upon the carotid sheath on this day had

absolutely no effect, whereas on the previous occasion, when the patient was under the influence of digitalis, the carotid pulsation could be scarcely felt without producing conspicuous slowing of the pulse.*

Description of electrocardiograms. The figures which are published in illustration of this case may be described most conveniently without reference to their chronological order.

Fig. 21 was taken after the resumption of the normal rhythm. The photograph consists of one strip of curve from each lead, and each strip contains a solitary premature contraction, springing from the auricle. In lead *I*, the auricular contractions of the normal cycle are represented by two small pointed summits (marked *x x* in the figure). The auricular contraction of the premature cycle is represented by a single pointed summit (marked *P* below the line). In leads *II* and *III*, also, the premature auricular summits differ in outline from those of the normal cycle. Fig. 21 consequently shows a normal rhythm, interrupted by premature auricular contractions which arise in an ectopic focus.

The interpretation of Fig. 20 is equally clear. Comparing the curves with the series in which normal cycles are present, it is evident that co-ordinate contraction of the auricle is in abeyance, for there is no sign of the presystolic *P* summits of Fig. 21. On the other hand, the ventricular action is slow and extremely irregular; prominent oscillations characteristic of a fibrillating auricle are present.

Fig. 17 shows the curves obtained from the three leads while the heart was beating regularly, and while 4 : 1 heart-block was present. The outlines of all the auricular waves may be clearly distinguished in leads *II* and *III*. In lead *I*, the outline of two *P* summits are easily recognised in each pause, the remaining *P* summits, of which there are two to each cycle, fall with *R* and *T* respectively. The auricular summit has the same form as has that of the premature beat in Fig. 21 *I*. The *P* representative of leads *II* and *III* form a continuous series, so that the string is never at rest. The activity of the auricle appears to be continual; the rest between the beats is absent or inappreciable in duration. The relation of the *P* summits, in leads *II* and *III*, to the deflection of the string produced by ventricular systole, are seen to advantage in Fig. 19. The curve was taken with the string standardised to give a deflection of $1\frac{1}{2}$ cm. to the millivolt, and at a faster speed than that at which the remainder of the curves were taken. The continuity of the auricular representatives is broken by the ventricular deflections, but for one cycle in each of these curves, the auricular portion of the electrocardiogram has been reconstructed, by drawing upon the original curve, so as to make the relation of the auricular and ventricular portions of it evident. The unvarying, regular and rapid beating of the auricle, displayed in this fashion, is also exposed in Fig. 18, taken on the same

* The patient returned with a new paroxysm on February the 24th, 1912. It was of the type seen in Fig. 15.

day. The right carotid sheath and the contained vagus were pressed upon, at or about the time at which the curve commences. Two ventricular cycles, belonging to a period of regular 4 : 1 heart-block are shown : the ventricle ceases to beat for 18 auricular cycles under the influence of the stimulation of the vagus : following upon the release of compression the preceding mechanism, *i.e.* 4 : 1 heart-block, is rapidly restored.

A few days before Fig. 17 was secured, that which is shown in Fig. 16 was obtained. A comparison of the two figures renders detailed description unnecessary ; it is evident that a varying degree of heart-block is exhibited, while the auricular rate is continuously rapid. Periods of 2 : 1 and 4 : 1 heart-block are mixed together.

It is from a careful consideration of the curves, which have been described, that the interpretation of Fig. 15 becomes clear. The beating of the ventricle is approximately at 146 beats per minute ; in Fig. 17, the ventricular action is but about half this rate. It is Fig. 17, and the transition curve (Fig. 16), which suggests so strongly that the rapid auricular action is continued throughout the whole series (namely, Fig. 15, 16 and 17). Fig. 15 is important because it shows the picture presented by the patient when first seen. A correct interpretation of this isolated curve would be difficult or impossible. Yet with the full series of curves in view, it is a matter of no great difficulty. The little *P* summits, two to each ventricular contraction are clearly distinguishable in lead *I*. In Fig 19, leads *II* and *III*, the auricular activity is represented by a continuous wavy line. The same form of electric disturbance may be followed throughout leads *II* and *III* of Fig. 15, though in this instance it is broken more frequently by ventricular deflections.

Additional cases of rapid auricular action. The interpretation of this series of curves has thrown considerable light upon a number of isolated curves in my collection. One of them has been published recently by Dr. Mackenzie in this journal,¹¹ but its interpretation was not possible at that time. With his permission, I republish it as Fig. 23 of the present communication and am now able to place the companion curve, namely, that showing the normal heart action in the same case, side by side with it (Fig. 22). The small and upright *P* summits of lead *I* (Fig. 23) are quite evident and are regularly spaced ; the deep inverted deflections of leads *II* and *III* are also evenly spaced and are now equally evident. The rate of the auricular contractions in this curve is approximately 320 per minute. The patient, as the original account of him tells, was the subject of paroxysms of tachycardia of two forms. In one the pulse beat at 140-150 per minute, in the other the pulse was observed to mount to rates of 280 and 300 per minute. The explanation of these rates is now apparent ; during the slower paroxysm, 2 : 1 heart-block was present ; during the faster paroxysm it vanished.

Two other patients, from whom I have obtained electrocardiograms, during attacks of tachycardia, have shown similar phenomena. The curves

of these two patients are so much alike that a single illustration will suffice for both.

Electrocardiograms are shown in Fig. 24, in which auricular contractions are clearly represented in all leads, the *P* deflections occur twice as frequently as do those of the ventricle. The rate of auricular contractions is 313 per minute, while that of the ventricle is 156.5 per minute. The curves were taken from a patient in whom the rate is said to have been maintained* for a period of three years. Under a full course of digitalis, the fast and regular auricular action has since given place, first to fibrillation, and later to the normal rhythm.

In the fourth case, which I have personally examined, the rate of auricle and ventricle were 260 and 130 respectively.†

Discussion. Several instances of very rapid and regular action of the auricle have been recently placed on record. Notable examples of the phenomenon are Hertz and Goodhart's case;³ that more recently described by Jolly and Ritchie,⁵ and the three cases described by Rihl;¹² in these five patients the highest recorded rates of auricular contraction were 236, 300, 315, 222 and 214, respectively. In all these cases heart-block was also present at some period of the observations, so that the ventricular rate was but a fraction of the auricular. To these records I am able to add Mackenzie's case¹¹ and a new series of three cases; it will be evident that the condition is not so rare as might have been supposed, and it becomes clear that many of the older accounts, which state that paroxysms of tachycardia may be accompanied by ventricular rates of from 200 to 300 per minute, are no longer open to the scepticism with which they have hitherto been regarded, in the absence of graphic records. The sudden and exact doubling of already accelerated ventricular action, such as has been described by Hoffmann,⁴ also receives a ready explanation. The "Auricular flutter" as Jolly and Ritchie have named it, is commonly associated with heart-block, the degree of which may vary, producing halved ventricular rate from time to time.

The recognition of a type of paroxysmal tachycardia in which extreme rates of auricular contraction are maintained, is of considerable importance, for such patients are ever on the verge of developing auricular fibrillation; and, as Mackenzie has pointed out, the production of fibrillation may be beneficial; not only is the heart rate reduced at its onset, but by the abolition of the accelerated and regular action of the auricle, the restoration of the normal rhythm may be hastened. Of the three cases which I have added to the published series, two have reacted at the administration of digitalis, and the auricle has passed into fibrillation. In both of these the normal rhythm was restored soon after the administration of the drug ceased. The third case passed from observation before the action of the drug could be

* For this information and that which follows I am indebted to Dr. Blackburn of West Hartlepool.

† Three additional cases have since been observed. The rates of auricle and ventricle were 320 and 160, 224 and 112, 334 and 167, respectively.

tested. In Mackenzie's case fibrillation was produced by digitalis and the normal rhythm was subsequently restored. The auricle also passed into fibrillation in one of Rihl's cases.

A brief description of the polygraphic curves, which these patients yield during periods of auricular acceleration, is desirable. In some the records are clear, as in the patients of Hertz and Goodhart, and those of Jolly and Ritchie; much more frequently they are obscure. In the four cases which I have seen personally, and in an additional case from which I have seen the polygraphic tracings alone, the venous records were anything but easy to read. The auricular summits are often small and inconspicuous, and many of the curves have waves which might readily be misinterpreted as *a*, *c* and *v*, three such waves commonly occurring with each ventricular cycle. An example is shown in Fig. 6, a curve taken from the case which has

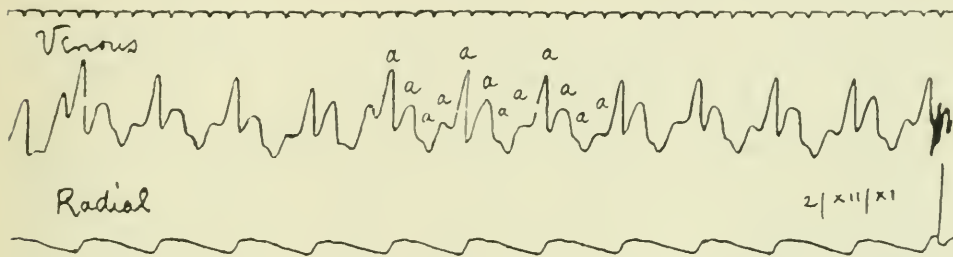


Fig. 6. A polygraphic curve during a period of 4:1 heart-block. The venous curve consists entirely of *a* waves; though, in the absence of electrocardiograms, they would be mistaken for *a*, *c* and *v* waves accompanying each ventricular cycle. The corresponding electrocardiogram is shown in Fig. 17.

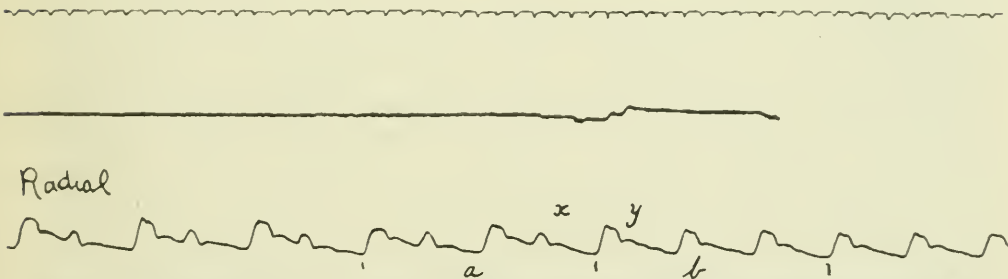


Fig. 7. A radial curve from the same patient, showing the passage from a period of 2:1, 4:1 heart-block into a period of 4:1 heart-block. The interpretation of the curve is known from comparison with such electrocardiograms as that shown in Fig. 16.

The presence of heart-block may be determined from the radial curve itself, by noting the shortness of the pause *x* as compared with the pause *y*, and by noting the equality of the two periods *a* and *b*.

been fully described in the present paper. The radial pulse is beating regularly at 73 per minute, a rate which it maintained for many days. There is little in the venous curve to guide the observer to the true condition of the auricle, which as we know, from the corresponding electrocardiographic curve (Fig. 17), was beating at the time when this curve was taken at the rate

of 292 per minute. Very considerable help may be obtained in the interpretation of such curves from a careful study of arterial tracings. A curve, such as is shown in Fig. 7, does not represent the passage of a period of bigeminy (resulting from premature contractions) into the normal rhythm; if that were so the length of the cycle x would not be conspicuously shorter than the cycle y . Such curves are given by heart-block alone. The clue to the actual mechanism which produced this curve is given by a comparison of the periods a and b . They are exactly equal, yet one contains four cycles while the other contains *three*. Assuming a constant auricular rate throughout, the proportion between the number of responses over the period a and over the period b should be as 4 is to 3. This proportion is only fulfilled by two conditions, (1) the passage of a 1 : 1, 2 : 1 ratio into a 2 : 1 ratio, or by (2) the passage of a 2 : 1, 4 : 1 ratio into a 4 : 1 ratio. One or other of these conditions would, I think, alone account for the curve as it stands. Further than this the analysis could not be taken, upon the evidence of this radial curve alone; but the electrocardiogram taken on the same day, Fig. 16, shows that the second interpretation is the correct one; the mixture of 2 : 1 and 4 : 1 periods is clearly demonstrated in this curve.

Thus, the group of cases considered is of importance because, in the absence of electrocardiographic curves, the high frequency of auricular contractions may remain unsuspected. In the case which I have described in detail, the pulse rate was for several days within the normal limits, and usually its rate was 75. Yet the rapid auricular action (280-300) was maintained throughout the whole of this period, and neither the skiagraphic examination of the chest, nor the employment of the polygraph was sufficient to reveal its presence.

Finally, I may again draw attention to the action of the auricle in cases where the rate of its contractions is raised phenomenally. As I have already determined, by an examination of the electrocardiograms of ten patients during the period of tachycardia and by a comparison of these curves with those of normal or quiescent periods the shape of the auricular summits proves that the new rhythm originates, not at the pacemaker, but in some new auricular focus. The same statement applies to instances of tachycardia in which rates of 300 are approached, as shown by the present series. The comparison of the P summits during the period of tachycardia and while the normal mechanism is present is possible in Fig. 17 and 21 and in Fig. 22 and 23. That the site of impulse formation, in the patients from whom Fig. 17 and 23 were obtained, was *ectopic*, is evident from the abnormal shape of the P summits, as compared to the normal, while the tachycardia is present. That it was also ectopic, in the case which is illustrated by Fig. 24, is evident from the outlines of the summits in leads *II* and *III*. In both these leads P is inverted. Similar pictures were obtained from the fourth patient. Electrocardiograms were obtained in Jolly and Ritchie's patient and also in Rihl's; and though a comparison with the curves of the normal mechanism is not possible, where they are concerned, it is probable that in

these instances also, a new site of impulse formation had developed. It consequently seems clear that instances of accelerated auricular action to rates of 250 or 300 are usually, if not always, associated with displacement of the centre of impulse formation. As in patients who exhibit slower paroxysms of tachycardia, the new rhythms are ectopic.

PART II.

ANOMALOUS VENTRICULAR ELECTRIC COMPLEXES OF SUPRAVENTRICULAR ORIGIN; ABERRANT VENTRICULAR CONTRACTIONS.

In previous articles, I have impressed the importance of the principle, that in the interpretation of electrocardiographic tracings, the shape of the curve is controlled by the direction taken by the contraction wave. When an impulse descends to the ventricle along the normal path and enters the musculature of this chamber through the *normal field of reception*, namely, the arborisations of the auriculo-ventricular bundle, the anticipation is that it will give rise to a contraction, which yields a ventricular complex of a definite and recognised form, namely, that which is regarded as physiological. And this anticipation is realised under most circumstances, be they experimental or clinical. But the rule is not without important exceptions. It occasionally happens, as in the case reported at an earlier date,⁷ that impulses which can be shown to be of supraventricular origin give rise to contractions yielding ventricular complexes of anomalous outline.

The case from which the original curves were taken is still under observation and has been repeatedly re-examined. The patient is the subject of paroxysmal tachycardia, and numerous premature contractions of auricular origin interrupt the slow periods. The origin of the premature auricular contractions has remained constant for an observed period of two years. This conclusion is based upon the shape of the electric complex, which represents the prematurely contracting auricle. The usual peak *P*, of the rhythmic beats, is replaced by a small and inverted summit; a summit which has maintained a uniform outline for the period named.*

But while the premature auricular complex has remained uniform, the complex accompanying the succeeding ventricular contraction has been of three distinct forms. For the convenience of description I rename these complexes, types *A*, *B* and *C*. Type *A* is a ventricular complex of normal

* In the original paper, the inverted summit was interpreted to result from an ectopic beat, or one arising at a point lying at a distance from the pacemaker; and this interpretation was based upon experimental observations which have recently been criticised by Rothberger and Winterberg.¹¹ If various points of the auricular surface are stimulated, the auricular complex is of a different but definite form with each separate stimulation. Rothberger and Winterberg consider that this may be due in some measure to escape of the stimulating current, and state that they have been unable to avoid this escape. Personally I have had no such difficulty since I have used closely approximated electrodes, and may state quite emphatically that such complication of the curves is quite a rare event, but that if it does occur, it is readily recognised, and should not confuse the interpretation of curves.

outline, being of the same shape as the ventricular complex of a rhythmic beat. The ventricular complexes of premature contractions arising in the auricle correspond in most patients to type *A*; an example is shown in Fig. 8 of the present paper. It is to the divergent types that I desire to draw attention at the present time. Types *B* and *C* are shown in Fig. 25. This figure consists of twelve curves, arranged in four vertical columns, each containing the pictures of Einthoven's three leads (marked *I*, *II* and *III* respectively in the figure and arranged in three corresponding horizontal rows). The two central vertical columns (*b* and *c*) of the figure show the curves from the patient already referred to, and the two curves from lead *II* are those originally published. In both curves a couple is shown consisting of a single beat of the normal rhythm and a premature beat. In both instances *T* of the rhythmic beat is notched by the inverted auricular peak (marked *P* below the line), and it is followed by an anomalous ventricular complex. In the particular patient of whom I speak, these anomalous complexes have occurred very frequently, and they have often alternated with each other, from couple to couple.

I have made a large number of observations in the hope of obtaining the corresponding pictures in leads *I* and *III*, but have been only partially successful. There has been no difficulty in obtaining the complete set of six curves; but it has not been easy to identify the curves of leads *I* and *III* with types *B* and *C* as they are seen in lead *II*, for the reason that both types occur in a single patient. When a continuous bigeminy, *including beats of one or other type alone, has been seen*, the lead has been rapidly changed by means of a special key devised for the purpose, and successive strips have been taken of the several leads. In regard to lead *III*, no doubt remains that the beats corresponding to type *B* and *C* of lead *II* are correctly placed in the present figure, but as regards lead *I* this correspondence has not been so conclusively demonstrated, though I believe that here too the arrangement as depicted is the true one. For the time being, we may assume that curves *I*, *II* and *III*, as they are arranged in columns *b* and *c* of Fig. 25, correspond to the complexes *B* and *C* in the respective leads of Einthoven.

I may now describe the curves of columns *a* and *d*. In column *a*, curves from leads *I*, *II* and *III* are shown. They were taken from another case exhibiting paroxysms of tachycardia of auricular origin. In this case, also, anomalous ventricular complexes interrupted the slow periods, and they correspond to the ventricular contractions of beats arising prematurely in the auricle. The premature auricle, in leads *I* and *II*, has much the same form as that of the rhythmic beats; in lead *III* it consists of several small variations. In each lead it is followed by an anomalous ventricular complex, and the shapes of these complexes are very similar to those illustrated by the corresponding leads of column *b*.

Next let us examine column *d*. In this column are three curves from a patient who has been under observation for a year or more. The patient's heart has been irregular as a result of the presence of premature auricular

contractions for the whole of this period. Three leads are shown; each curve consists of two coupled beats, the second of which is premature. The ventricular complexes are anomalous,* though the corresponding contractions are of supraventricular (in this case, auricular) origin. The three pictures of this column (*d*) are very similar to those of column *c*.

Thus three patients have been observed in whom anomalous ventricular complexes have been found to accompany premature auricular contractions; in one (column *a*) the complexes were of type *B*; in another (column *d*) they were of type *C*; in another (columns *b* and *c*) they were of types *B* and *C*.

Treating the cases singly, the first fact which merits attention is that in all three cases, each repeatedly examined, the type of anomalous complex has been constant.† This constancy of outline from month to month and year to year is especially noteworthy. The mechanism by which such beats are produced is constant, and its constancy suggests its comparative simplicity. The view that the mechanism is a simple one receives additional and strong support when the cases are treated collectively; curves of almost exactly similar type occur in distinct cases.‡

Before proceeding to the statement of a hypothesis by which the occurrence of these anomalous beats may be explained, it may be well to summarize briefly our knowledge of them.

In the present communication it has been stated that (1) they yield uniform electric effects in given patients over long periods, and it has been shown that (2) the same distinctive types are met with in different patients. In a previous communication⁸ I have shown that (3) type *C* may also occur in experiment and that (4) it is independent of the point of origin of the impulse, providing that the latter arises above the ventricle. (5) The abnormal types are always associated with demonstrable alterations of conduction in the tissues uniting auricle and ventricle. Occasional or continued prolongation of the *P-R* interval has been found in each and all of the patients in whom they have been observed,§ and also in the dog in which they were seen.

The recognition of these conduction changes in the patients considered may necessitate repeated examination. They may not be in evidence at the first or even the second or third examination; but they are eventually found.

A characteristic example of the phenomenon has been recently recorded by my former assistant Dr. Leo Rosenthal.¹³

Surveying these facts, and remembering how the shape of an electric curve is controlled by the direction of the contraction wave, one hypothesis

* The patient presented these anomalous complexes on occasion only. They were usually of type *A* (Fig. 8 & 9 are from the same case).

† Within certain limits to which subsequent reference will be made.

‡ Type *B* has been figured by Kraus and Nicolai.⁶ These authors have attempted to associate it, though upon insufficient grounds, with a beat of atrio-ventricular origin.

§ Five patients altogether. A prolongation of interval is seen in lead *II*, Fig. 25, column *a*, of one of the new cases here described.

alone seems adequate in explanation of them. It is suggested that they may be due to damage affecting *special* branches of the auriculo-ventricular arborisation, and that this damage is such that a block is present; so that, at one time, the impulse is transmitted through the whole arborisation, while at other times, it passes into the arborisation, but fails to course along certain given channels.

But before this hypothesis can be accepted, an observation remains, with which it must be reconciled. A series of curves was published from the original case, in a previous article to this journal,⁸ which showed a complete transition from the normal type (type *A*) to type *C*. I am now able to publish a second though less perfect series. Two curves are shown in Fig. 26. They are from the same case as those of column *d* of the last figure. Both are from lead *II*. The second and premature beat of the top curve in Fig. 26 has a ventricular complex of type *A*. The premature beat of the bottom curve (Fig. 26) is transitional between type *A* and type *C* (Fig. 25, column *d*, lead *II*). Special attention is drawn to the intervals in these three curves. *Proceeding from type A to type C, the prematurity of the second beat of the couple increases; the shorter the interval intervening between normal and anomalous beats, the greater is the divergence of type.* A precisely similar observation was made in the instance formerly published;⁸ and the anomalous beats were seen in experiment, only when this interval was short. We may continue the previous summary by stating that (6) the anomalous beats show transitions and that (7) they are most in evidence when the ventricular contractions to which they belong follow the preceding contractions at short intervals.*

The prematurity of the contraction influences the type of complex because the recovery of conduction is dependent upon the interval of rest which precedes the contraction with which it is associated.

How may the transition types be explained? I assume that a given anomalous complex, in its fully developed form, results from a complete obstruction to the passage of the impulse along certain definite branches of the arborisation. The transition forms are explained if it is assumed that during the progress of certain beats, there is delay in the passage of the impulse along the same branches of the arborisation; and according as the delay is small or great, so the complex will approach more closely to type *A* or type *C*.

I may illustrate and support this conception by describing the accompanying figure, an experimental curve. Fig. 27 shows myocardiograms (*A* and *V*) from auricle and ventricle respectively, an electrocardiogram, a time-marker and signal of stimulation. The stimulation was repeated at rhythmic intervals, the rate of stimulation being slightly in excess of the heart rate, and the point of application being the left margin of the ventricle

* Similar changes accompany increase of heart rate, notably in paroxysms of tachycardia; a fact which has been discussed in my book "The Mechanism of the Heart Beat," London, 1911, page 180.

near its apex. The first two stimuli fall, as shown by the vertical lines drawn from the signal, in the refractory period of the ventricle. The third falls just before the commencement of the refractory state; the fourth a little earlier and so on. Each falls *subsequent to the commencement of an auricular contraction*. Thus in each cycle two contractions waves are started, one naturally and from the auricle, the other artificially and from the apex of the ventricle. According as one or other is precedent so it governs the ultimate type of the ventricular contraction. In the fourth cycle of the figure, the ventricular contraction is almost a pure response to the supraventricular impulse. In the last cycle of the figure, the ventricular contraction is a pure response to apical stimulation. Between them lies a perfect transition series, and this transition series is the result of a gradual alteration of the times at which the impulses reach the several portions of the ventricular muscle mass. A gradually increasing delay in the conduction of purely supraventricular impulses, through a limited division of the arborisation, will produce a comparable series of transition curves; and such is the explanation offered of the clinical electrocardiograms which have been discussed.

As final illustrations of the phenomenon for which I propose the term "aberration of the supraventricular impulse" or "aberration" I may cite certain experiments upon asphyxial heart-block.

In conjunction with Mathison⁹ I have shown that all the known stages of auriculo-ventricular heart-block may be produced in cats by a simple process of asphyxiation, but we were unable to demonstrate that the block is produced as a result of poisoning of the special junctional tissues. Evidence for this is now forthcoming, thanks to the observations of Eppinger and Rothberger.² These workers have demonstrated that separate section of the left and right main branches of the auriculo-ventricular bundle is followed by beats of the ventricle which start in right or left ventricle, respectively. Such beats, which are unquestionably aberrant, in the sense in which I use the term, give rise to electric curves, which correspond to the recognised complexes of premature ventricular beats, started in the right and basal portion of the heart or left and apical portion of the heart respectively.

It not infrequently happens that similar pictures are obtained from the asphyxiated cat. Perhaps, as in Fig. 28, 2:1 heart-block is present, when suddenly the normal ventricular complex gives place to one which is recognised as corresponding to a contraction started in one or other side of the heart (in the instance figured it is from the right and basal portion of the ventricle).^{*} Very many interesting curves are produced in this manner and they suggest that the products of asphyxia act, not only on the junctional tissues as a whole, but also to a varying extent on the several portions of this system. Transitional curves between the normal and a fully aberrant type

^{*} Very similar curves have been recently published by Einthoven,¹ who produced them experimentally by stimulating the vagus.

are surely to be anticipated under these circumstances, and I publish the last figure as a probable example of the phenomenon. The curve shows the passage of a period in which there is prolongation of the *P-R* interval to what is apparently complete dissociation. The type of ventricular complex suddenly changes from the normal (*R, T'*) to that of a beat starting in the left or apical portions of the ventricle. From this point onwards there is a complete transition from the large diphasic complex to the normal complex, which is seen at the end of the curve. In explanation of this curve I suggest first that at the point of the primary change, complete dissociation supervened as a result of poisoning of the main bundle; and that the bundle directly below the seat of functional damage became at that moment pacemaker to the ventricle. So far the explanation is in accord with all previous observation. I suggest further that the mechanism was complicated by the simultaneous onset of functional damage to the right branch of the bundle. The first impulse discharged from the ventricular pacemaker consequently travelled along the *left* branch alone. At the second discharge, the impulse travelled along the left branch, and after considerable delay, also along the right branch. At the third discharge the delay in the right branch was less, at the fourth less still, until at the discharge which created the last beat represented in the curve, conduction was again equal on the two sides.

SUMMARY OF PART I.

1. The auricular contraction which follows a premature auricular contraction, may arise from the same focus as the premature beat. The phenomenon is considered to be the result of slight quickening of physiological impulse formation in the area in which the premature beat arises. (Section 1.)

2. A clinical instance of premature auricular contractions, followed by pauses, which are considerably shorter than the interval between rhythmic beats, is described. It is probable that the premature beats originated in, or near, the pacemaker; the shortening is referred to acceleration of impulse formation in the pacemaker, as a result of the origin of premature beats in it, or in its neighbourhood. (Section 2.)

3. The direct and repeated change of regular and accelerated auricular action to auricular fibrillation and back again is recorded (Section 3). Another case, in which an ectopic auricular rhythm was converted into fibrillation by the action of digitalis, receives detailed description (Section 4). Several additional cases of a similar nature are described (Section 4). The observations show the close inter-relation of paroxysms of regular tachycardia, arising in the auricle, and auricular fibrillation.

4. An instance of auricular fibrillation, in which the ventricle beat at 90 per minute, and in which its action was perfectly regular, is placed on record. The regularity of the ventricular action is ascribed to the presence of complete heart-block, brought about by digitalis administration. Another, and somewhat similar case, is referred to (Section 3).

5. An instance of unexpected death in a patient, whose curves had shown auricular fibrillation and premature ventricular contractions a few hours previously, is recorded. Death is attributed to ventricular fibrillation. (Section 3.)

6. A patient who came under observation with a ventricular rate of 150, and an auricular rate of 300, is recorded; electrocardiograms from two similar cases, in both of which 2:1 heart-block was present, and in which the rate of auricular contractions reached 320 and 315 per minute, are also described. Extreme acceleration of the auricle, to 300 per minute, does not seem to be an uncommon condition: several other instances are spoken of. Heart-block usually accompanies the condition, so that the acceleration in the ventricle is not of like degree. (Section 4.)

7. The exact doubling of rate in paroxysmal tachycardia, described by Hoffmann, is probably referable to the relief of heart-block of 2:1 grade. (Section 4.)

8. Extreme acceleration of the auricular rate usually gives place, sooner or later, and especially as a reaction to digitalis, to fibrillation. The normal rhythm is often restored subsequently. Digitalis medication is of considerable value in such cases, either by reducing the ventricular rate, or by ultimately aiding the restoration of the normal rhythm. (Section 4.)

9. When auricular acceleration is accompanied by heart-block, and fibrillation sets in, at the onset of the latter the ventricular rate is lowered. (Section 4.)

10. Extreme acceleration of the auricular contraction rate is the result of new and ectopic impulse formation in that chamber. Four new examples are cited as evidence of this statement. (Section 4.)

11. The polygraphic curves obtained from patients, in whom the auricular contraction rate shows extreme acceleration, are often deceptive. They may easily be mistaken for curves given by a normally beating heart; the electrocardiographic examination may be the sole means of detecting the true nature of the heart's mechanism. (Section 4.)

12. An instance of pressure upon the right vagus nerve is described, in which heart-block was the sole result. The auricles continued to beat at the original rate, which was an extremely accelerated one.

SUMMARY OF PART II.

1. Several examples of anomalous electric complexes, accompanying the ventricular contractions of premature beats arising in the auricle, are described. It is shown that the anomalous complexes may be classed as distinct types, for the same types are encountered in separate individuals. This fact and the uniformity of their appearance in electric curves taken from isolated cases, from month to month and year to year, suggests that the mechanism of production is a comparatively simple one. In view of their constant association with demonstrable conduction changes in the

auriculo-ventricular junctional system as a whole, the hypothesis is put forward that they are due to disturbances of conduction in the smaller branches of this system; and it is held that definite branches are affected in this manner, though these branches cannot be identified at the present time.

It is proposed that the phenomena discussed should be termed "aberration of the supraventricular impulses" or more simply "aberration"; the anomalous beats may be conveniently spoken of as "aberrant beats" or "aberrant ventricular contractions."

2. There seems every prospect that, if this hypothesis be correct, it will be possible ultimately to identify lesions which affect not only the main divisions, but the smaller branches of the auriculo-ventricular bundle.

3. The products of asphyxia probably act in a selective manner upon the special tissues which serve the function of conducting impulses from auricle to ventricle.

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Fig. 11.

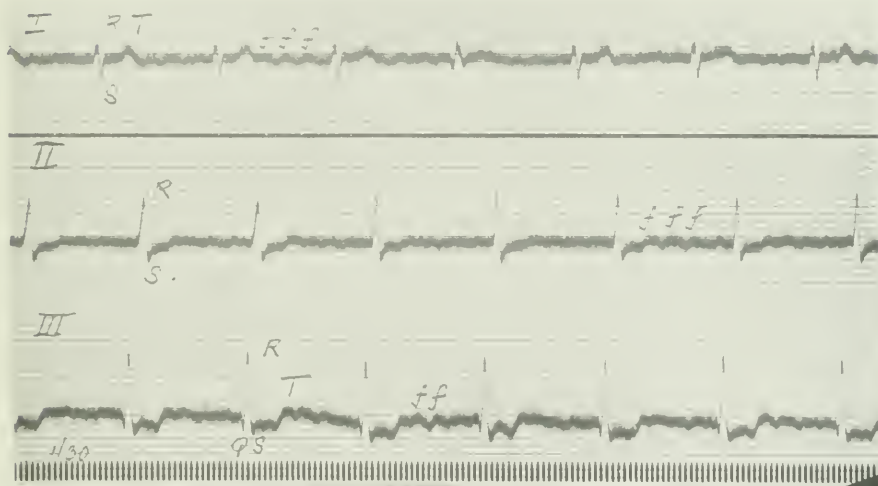


Fig. 12.

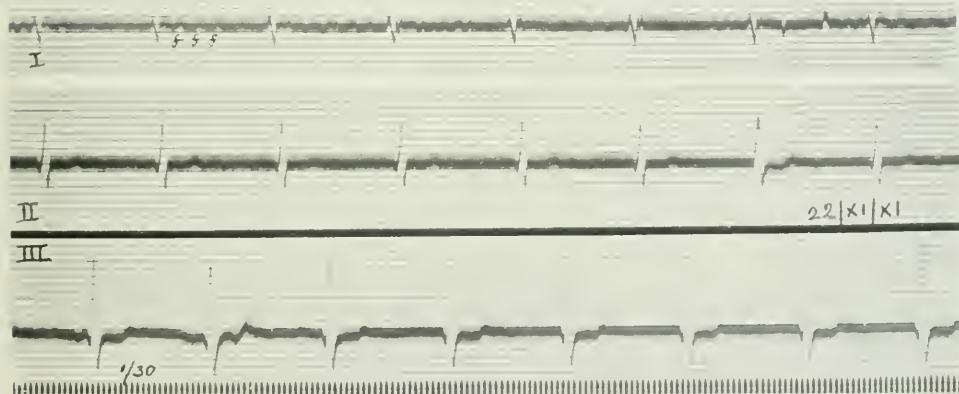


Fig. 13.

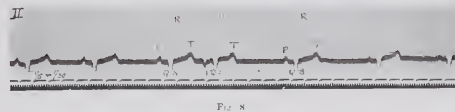


Fig. 8. An electrocardiogram from a lead *II* showing a single premature auricular contraction. The smallest *P*, corresponding to the premature beat, is marked. The time markers beat one-fifth and one-thirtieth seconds. The curve is standardised, so that one centimetre in a vertical direction is equivalent to one-thirtieth of a volt, (1 millimetre = 10^{-3} volts).

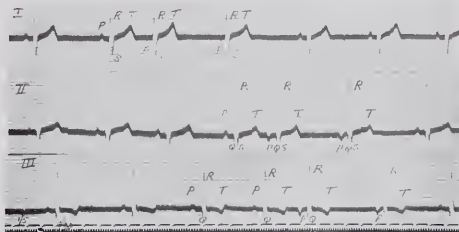


Fig. 9. An electrocardiogram from the three leads in the same case. Each shows a premature contraction arising in the auricle, but in each instance the first beat of the returning slow and regular rhythm arises in the same abnormal focus. The time marker beats one-fifth and one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-3} volts.

Fig. 10. *a* and *b*. Two electrocardiographic curves from lead *II*, which show premature contractions arising in the auricle at or near the pacemaker. Three premature contractions are shown: the auricular stimuli are marked *P* below the line. In one instance the premature beat is followed by a long pause; in the other two instances, by a pause which is considerably shorter (approximately by 13 seconds) than the pauses separating the following beats of the normal rhythm. Time marker beats one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-3} volts.

Fig. 11. Electrocardiograms from the three leads in a case of mitral stenosis, in which tachycardia of auricular origin was present. Time marker beats one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-3} volts.

Fig. 12. Electrocardiograms from the three leads, taken from the same case and showing the presence of auricular fibrillation, while the ventricle beats regularly at 90 per minute. Time marker beats one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-3} volts.

Fig. 13. Three electrocardiograms from the same case and on the same date, taken by means of special leads from the chest wall. *I*. The electrodes were placed in the fourth and fifth spaces directly to the right of the sternum: the oscillations are conspicuous. *II*. Taken from the outer end of the third left interspace and the apex lead: the oscillations are only just seen. *III*. Taken from the epigastrium and apex lead: the oscillations are scarcely visible. Time marker beats one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-3} volts.

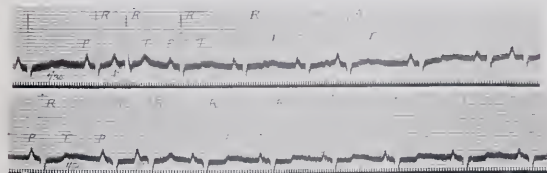


Fig. 10 (*a* and *b*).

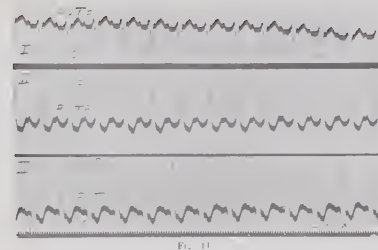


Fig. 11.

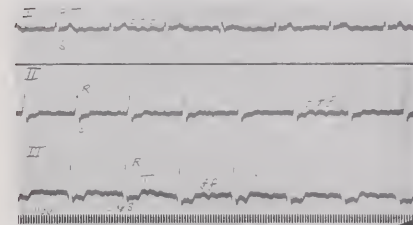


Fig. 12.

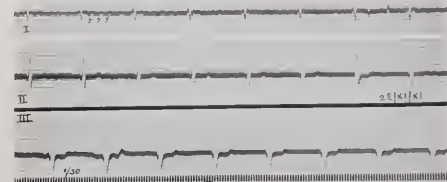


Fig. 13.

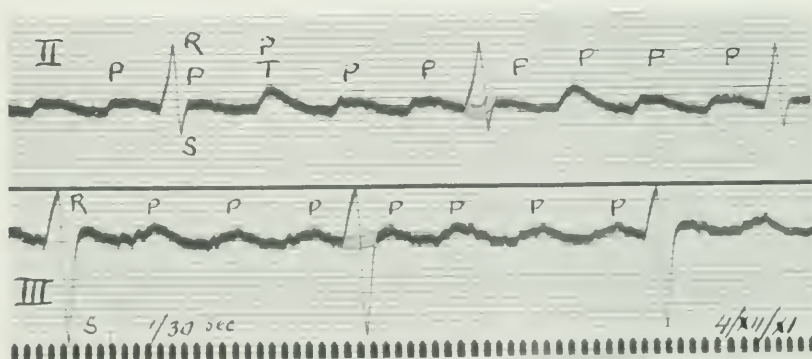
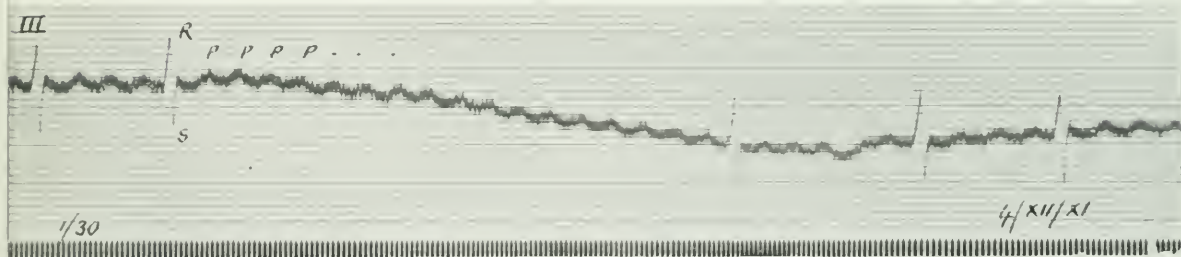
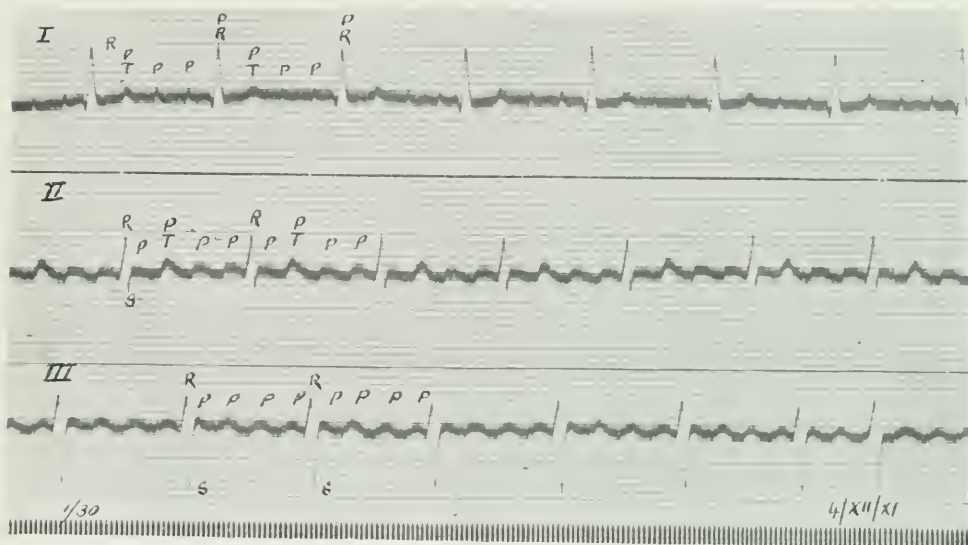


Fig. 14. The electrocardiograms from the same case, showing fibrillation of the ventricle with slow and irregular responses of the auricle. Devisional premature beats (*) are also present. Time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 15. Electrocardiograms from the three leads, showing an accelerated auricular action and 2:1 heart-block; the rate of the auricle is 200 per minute. Lead I is interrupted by a single ventricular contraction (V.R.). Time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 16. Electrocardiograms from the three leads, and from the same case, showing a further grade of heart-block. The curves show a mixture of 2:1 and 4:1 periods. Time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 17. Electrocardiograms from the three leads, and from the same case, showing 4:1 heart-block with a single 2:1 period in lead III. Time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 18. An electrocardiogram from lead III in the same case, showing the effect of pressing on the right carotid sheath. The ventricle fails to respond for 18 auricular cycles. The next response is after six cycles. Before and after the vagal compression 4:1 heart-block is present. The time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 19. Electrocardiograms from leads II and III in the same case. The curves are taken at a faster speed and the standardisation has been altered, so that the deflections are increased in amplitude. Three ventricular cycles are shown in each lead; the outline of the auricular cycles have been reconstructed, in each central cycle, by drawing upon the original curve. Time marker is in one-thirtieth seconds. Standardisation, 14 millimetres = 10^{-4} volts.

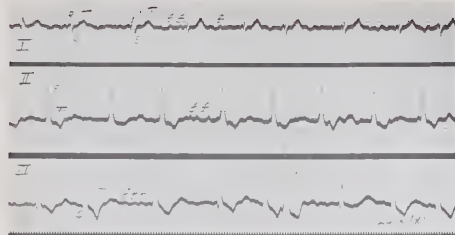


Fig. 14.

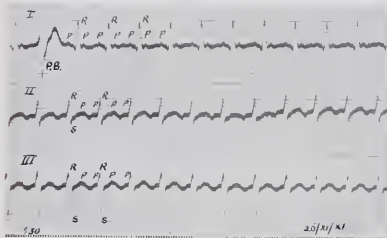


Fig. 15.

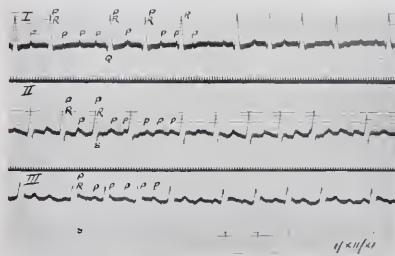


Fig. 16.

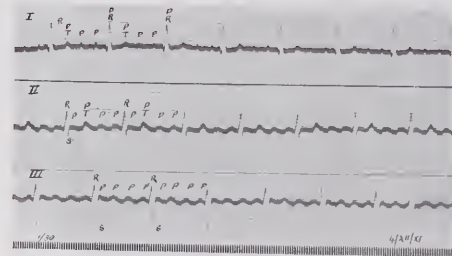


Fig. 17.

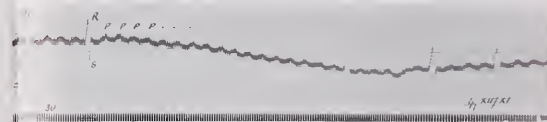


Fig. 18.

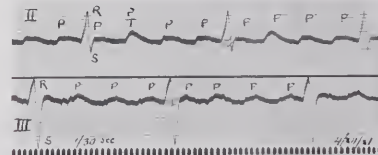


Fig. 19.

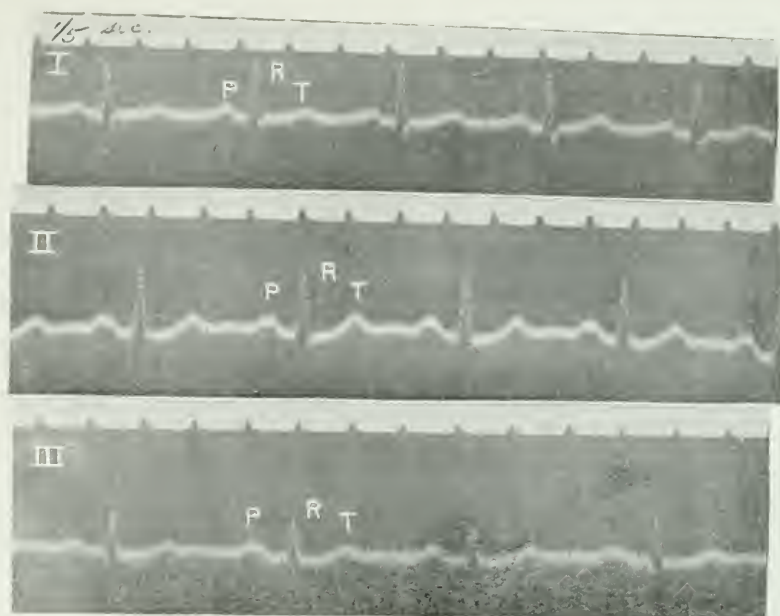


FIG 22

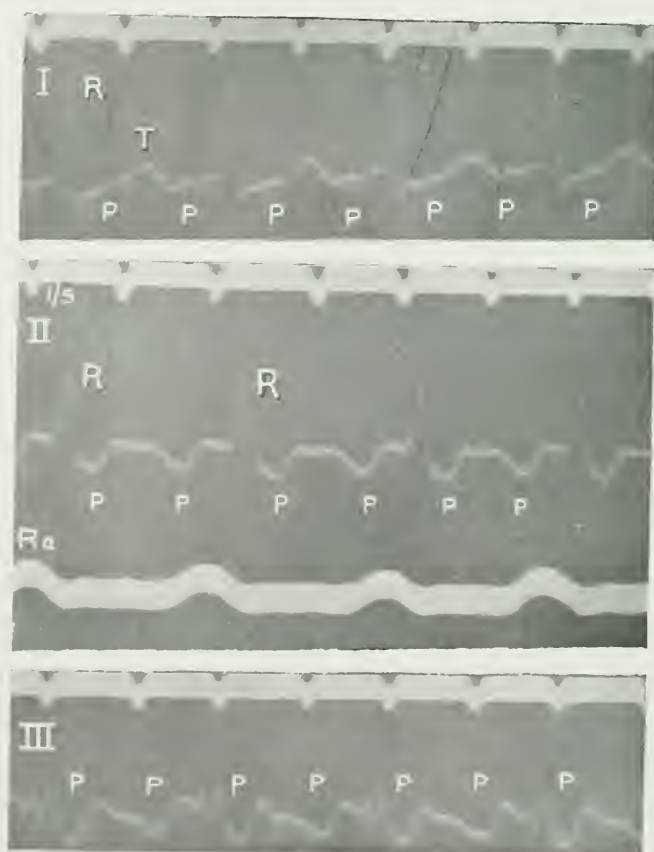


Fig. 23.

Fig. 20. Electrocardiograms from the three leads, and from the same case, showing the slow and irregular action of the ventricle in response to a fibrillating auricle. The time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 21. Electrocardiograms from the three leads and from the same case after the resumption of the normal rhythm. The regular beating of the heart is interrupted by premature contractions arising in the auricle. The ventricular deflections, *R* and *S*, have increased in their amplitudes. The time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 22. Electrocardiograms from the three leads in a case of paroxysmal tachycardia. The normal rhythm is present; each cycle consists of *P*, *R* and *T* waves. The time marker is in one-fifth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

Fig. 23. Reprinted from *Heart*, Vol. II, page 380. Three electrocardiograms from the same case during a period of tachycardia. Leads *I*, *II* and *III* are shown. The rate of the auricular contractions is 320 per minute; the rate of the ventricular contractions, 160 per minute. The time marker is in one-fifth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

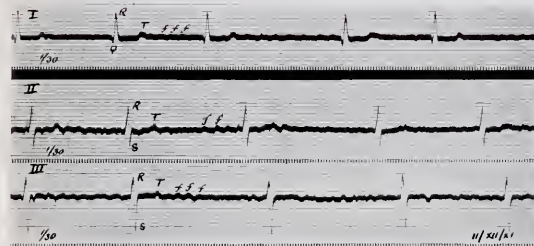


Fig. 20

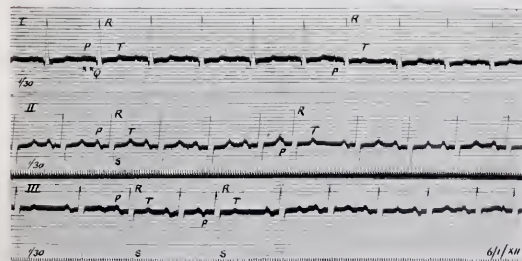


Fig. 21

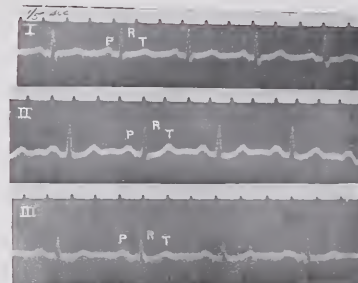


Fig. 22

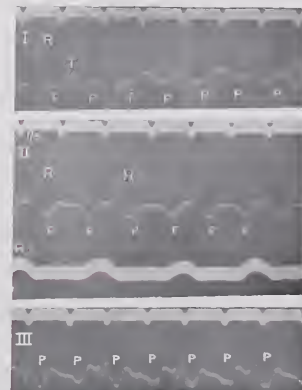


Fig. 23

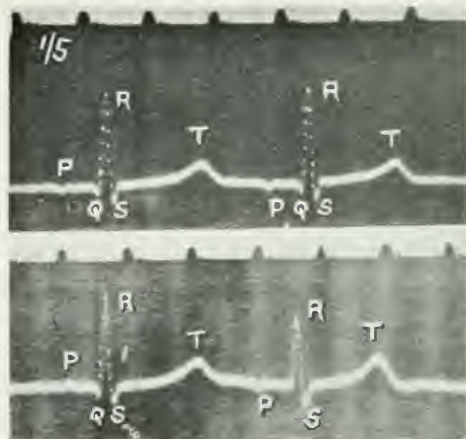


Fig. 24. Electrocardiogram at a rate of 315 per minute. Standardisation.

Fig. 26.

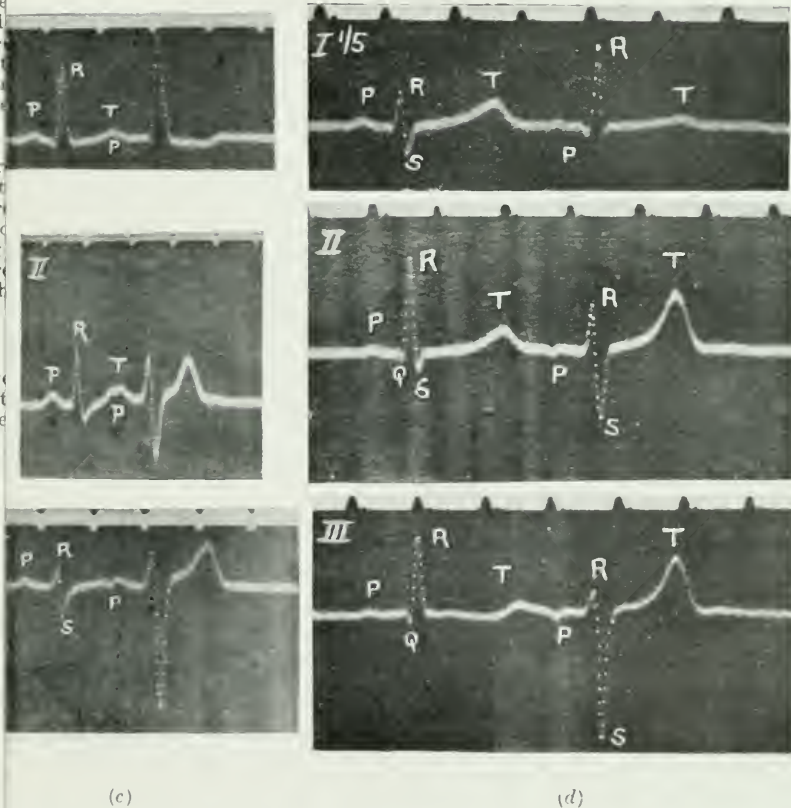
Fig. 25. This figure shows leads I, II and III. Column *a* shows the normal action. The time marker is in front of a second.

Columns *b* and *c* show previously recorded ventricular contraction and a premature contraction.

Column *d* shows a premature action resulting in a premature contraction.

Compare the results in columns *c* and *d*.

Fig. 26. Two curves from the same subject as in Fig. 25. A typical premature type.



(c)

(d)

Fig. 24. Electrocardiograms from the three leads in a case of tachycardia, showing an auricular rate of 315 per minute and 2:1 heart-block. The time marker is in one-thirtieth seconds. Standardisation, 1 millimetre = 10^{-4} volts.

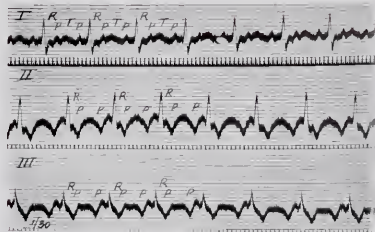


Fig. 24.

Fig. 25. This figure consists of four vertical columns, each consisting of three curves taken from leads I, II and III, respectively. The columns are marked a, b, c and d.

Column a consists of three curves from a patient suffering from paroxysmal tachycardia, and they show the premature auricular contractions which disturb the slow periods of heart action. The three curves are standardised so that 1 millimetre = 10^{-4} volts. The time marker is in fractions of a second, each pair of vertical lines correspond to one thirtieth of a second.

Columns b and c consist of six curves, taken from a case of paroxysmal tachycardia previously recorded. The curves are from the slow periods, and show two forms of "aberrant ventricular contractions" each in the three leads. Each curve consists of a rhythmic beat and a premature beat. The time marker is in one-fifth seconds.

Column d consists of three curves, taken from a patient, who has an irregular heart action resulting from premature auricular contractions. A couple consisting of a rhythmic and a premature beat is seen in each curve. The time marker is in one fifth seconds.

Compare the anomalous complexes of columns a and b and compare those of columns c and d.

Fig. 26. Two curves from lead II which form a series with the central curve of column d (Fig. 25). A transition is seen from the normal type of ventricular complex to the anomalous type. Time marker in one-fifth seconds.

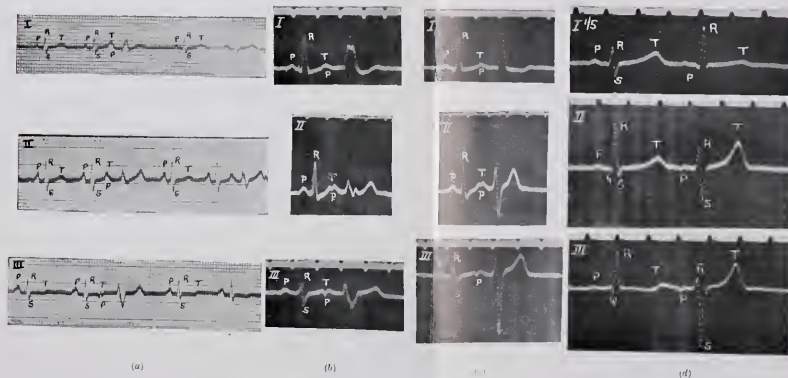


Fig. 25.

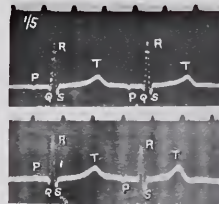


Fig. 26.

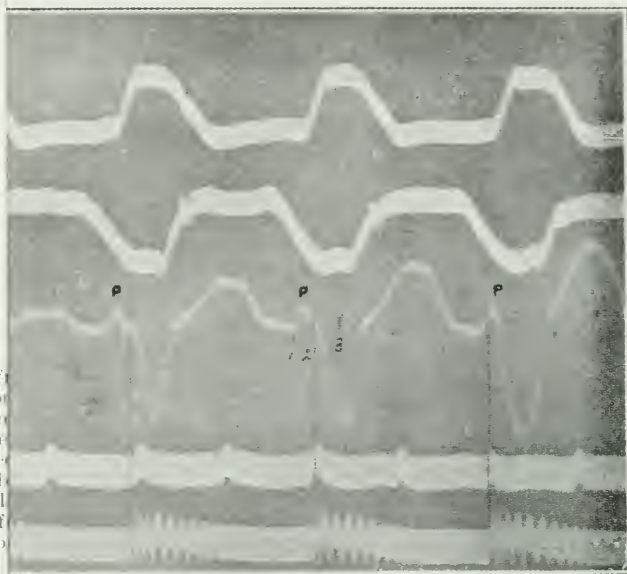


Fig. 27. (Reprinted from graphic curve from cardiogram. A time marker is shown in the figure. The velocity is slightly excessive. The waves are started by artificial stimulation. The natural impulse transition curves, for artificial stimulation

Fig. 28. An electrocardiogram showing a complete heart block. The type of stimulus reaching the heart is indicated by the time marker is in the figure.



Fig. 29. An electrocardiogram showing the P-R interval dissociation. The P waves and apical portions of the QRS complexes are of normal type again marked P in the figure.



Fig. 27. (Reprinted from *The Mechanism of the Heart Beat*, Fig. 126). *A*—myoeardiographic curve from auricle, *V*—myoeardiographic curve from ventricle, *E*—electrocardiogram. A time marker, beating one-fifth seconds, and signal of stimulation complete the figure. The ventricle was stimulated near its apex by a series of rhythmic impulses, at a rate slightly exceeding the rate of the auricular contractions. As a result, contraction waves are started both in auricle and in ventricle and they meet in the last named chamber. The natural impulses and artificial stimuli are so placed as to give a complete series of transition curves, from the normal type to that of a premature beat excited at the point of artificial stimulation. Time marker is in one-fifth seconds.

Fig. 28. An electrocardiogram from an asphyxiated and decapitated cat, showing 2:1 heart-block. The type of ventricular curve changes abruptly from the normal to that yielded by a stimulus reaching the right and basal portions of the ventricle alone. This has probably resulted from functional impairment of the left branch of the auriculo-ventricular bundle. Time marker is in one-fifth seconds.

Fig. 29. An electrocardiogram from an asphyxiated and decapitated cat. Three beats in which the *P-R* interval is prolonged are shown, and this condition passes into one of apparent dissociation. The first ventricular beat is of the form yielded by stimulation of the left and apical portions of the muscle; the succeeding beats show a complete transition to the normal type again. Traces of the independent auricular contractions are seen and are marked *P* in the curve. Time marker is in one-fifth seconds.

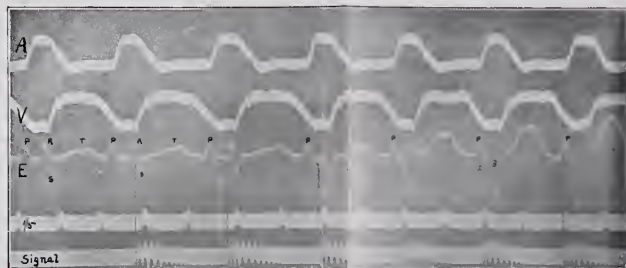


Fig. 27



Fig. 28.



Fig. 29.

THE ORIGIN OF CHRONIC ULCER OF THE STOMACH IN THE ACUTE VARIETY OF THE DISEASE

By CHARLES BOLTON

With Plates 23-26

FOR a considerable number of years, in fact from the time of Cruveilhier (1), two types of simple ulcer of the stomach have been recognized, the acute and the chronic.

In most text-books acute ulcer of the stomach receives very little attention, and sometimes it is absolutely ignored. Those authors who deal at all adequately with it treat it as being a disease quite distinct from chronic ulcer. In fact it is perhaps the general opinion that the two diseases have entirely different origins. Cruveilhier (2) initiated the idea that chronic ulcer arises from the acute variety, the initial lesion, in his opinion, being an inflammation of the gastric follicles occurring as a part of a generalized gastritis.

The term 'follicle' was formerly applied to the gastric glands, and was used in this sense by Abercrombie (3). Brinton (4) discusses the question and thinks 'it would be a great advantage if the terms "tube" and "follicle" were attached to distinct structures, the latter (as its etymology suggests) being restricted to the closed sac formed by the lenticular or solitary gland'. Carswell (5), in his book on Pathological Anatomy, uses the term 'follicle' to signify a lymphoid structure and gives an illustration of ulceration commencing in this situation. A perusal of his description of follicular ulceration leaves no doubt in the mind as to what Cruveilhier meant by the expression 'ulceration commencing in the lymphoid follicles of the stomach'. He likens these structures to the solitary follicles of the intestine and shows illustrations of enlargement of these lymphoid follicles in the stomach in cholera, which clearly demonstrate what he wished to imply by the term 'follicle'. He also describes typhoid fever as 'acute follicular enteritis'. Ulceration commencing in the lymphoid follicles of the stomach has therefore been recognized for almost a hundred years. Rokitsansky (6) also supported the view of the acute origin of chronic ulcer, but he thought that the ulcer commenced as a 'haemorrhagic erosion' or a 'circumscribed sloughing of the mucous membrane', and that it was 'in no way connected with gastritis'.

From time to time many observations have been recorded which appear to me to support the idea of the acute origin of chronic ulcer in greater or lesser degree.

The evidence obtained from these observations falls into several groups.

1. In chronic infective diseases, in which it is not uncommon for acute ulcers of the stomach to occur, there may sometimes be found ulcers with thickened edges and bases.

It might be questioned whether these thickened ulcers were actually due to the infections, but this supposition is rendered more certain in those cases in which both acute and thickened ulcers are found together in the same stomach.

In Cock's case (7) of diffuse inflammation of the leg, of several weeks' duration, there was found a superficial acute ulcer in both the duodenum and colon and an ulcer the size of a shilling on the small curvature of the stomach. It had chronic characters, the edges were smooth and raised and the base formed by the peritoneum.

Colombo (8) described three cases. In one case of gangrene of the leg and arm there were two ulcers present in the pyloric region of the stomach. Their bases were formed by the muscular coat of the organ and the peritoneum was thickened and adherent to the pancreas. In a second case of chronic dysentery there was a funnel-shaped ulcer of the posterior wall of the stomach with raised edges. In a third case of cancer of the uterus an ulcer of the stomach presenting chronic characters was found.

Dittrich (9) recorded two cases, one of chronic dysentery and the other of cancer of the uterus, in each of which there was an ulcer of the stomach having chronic characters.

Papellier (10) mentions two cases of chronic tuberculosis, in one of which were found some superficial lesions of the mucous membrane together with an ulcer on the posterior wall of the stomach near the small curvature. The ulcer was a quarter of an inch in diameter and had a fibroid base formed by thickened peritoneum. Four cicatrices were grouped around the ulcer. In the second case three ulcers were found in the pyloric region on the greater curvature. Two of the ulcers would just admit a pea and had recent black sloughs attached to their bases, whilst the third was older, had indurated edges, and penetrated to the peritoneum.

Chambers (11) also quotes a case of chronic phthisis in which three ulcers with raised and thickened edges were found on the middle of the smaller curvature of the stomach.

There cannot be any doubt that such cases are common enough, and that the ulcers showing these characters of chronicity were originally acute, and the result of the infective disease associated with them. Of course it is possible that a patient, the subject of chronic gastric ulcer, might acquire an infective disease, which would give rise to additional acute ulcers, but such a case should be readily recognized. For instance, the peritonitis resulting from the perforation of a chronic ulcer may give rise to acute ulcers in the mucous membrane.

There is a specimen in the museum at University College Hospital (*Medical Catalogue*, No. 3051 C) illustrating this point. The patient was operated upon for perforation of a chronic ulcer. He went on well for a few days and then died from a second perforation.

At the autopsy a large thickened chronic ulcer and several smaller ones, also old and thickened, were found on the smaller curvature of the stomach, one of which had given rise to the original perforation. A second series of ulcers was found lying near the greater curvature. They were all of the same age and acute, they were cleanly punched out, had blackened bases, and one had perforated. There is not the smallest doubt that this second series of acute ulcers resulted from the infection of the peritoneum caused by the first perforation.

The mere association, therefore, of acute with chronic ulcer in the same stomach by no means proves the acute origin of the chronic ulcer present. Still, it is not uncommon to find such an association in patients who are suffering from simple chronic ulcer and in whom no other cause than gastritis can be found to account for the acute ulcers as demonstrated by Nauwerck (12), Miller (13), and others. In such cases it appears to me that the origin of the chronic is identical with that of the acute ulcers.

Gerhardt (14) described three cases of gastritis in which he showed the connexion between 'erosions' and ulcers. On the other hand, Langerhans (15) quotes a case in which there were many small 'haemorrhagic erosions' and three large ulcers, with transitional forms between. He regards this as being a very exceptional case, as he thinks that chronic ulcers result from a primary affection of the blood-vessels in most cases, whilst catarrhal inflammation of the mucous membrane and crampy contractions of the stomach give rise to 'erosions' and very seldom to chronic ulcer.

It was Virchow (16) who originated the idea that spasm of the muscular coats of the stomach or portal stasis might cause haemorrhagic infiltrations into the mucous membrane and resulting ulcers. Key (17) continued this idea of venous stasis due to spasmodic contractions of the gastric walls, and Rindfleisch (18) considered that 'the act of vomiting, by temporarily arresting the return of blood, causes minute extravasations from the superficial venous radicles of the gastric mucous membrane', and that simple ulcer of the stomach originated in such haemorrhages. He quotes a case in support of this hypothesis in which several small haemorrhages, a larger circular haemorrhage, and a perfect simple ulcer of the same size were found after death. The case was one of strangulated hernia, so that the probable cause of the haemorrhages was not the act of vomiting but bacterial infection.

Bazy (19) also saw a case which showed all intermediate stages between superficial ulceration of the mucous membrane and typical ulcer. I am not concerned here with the particular kind of initial lesion that most frequently develops into chronic ulcer, because the material at hand is insufficient for this purpose, and such patients usually die with fully developed ulcers. I quote these few cases in support of the view that, whatever its origin may be, acute ulcer of the stomach is able to acquire chronic characters.

2. When a patient suffering from chronic ulcer of the stomach acquires an infective disease which is known to give rise to acute ulcer, it is not uncommon for the chronic ulcer to commence spreading acutely. In the recorded cases death

has occurred owing to a sudden attack of haematemesis, to perforative peritonitis, or to invasion of an organ, a thickened chronic ulcer being found at the autopsy. Thus Reimer (20) observed such a case during an attack of measles; Stareke (21) during pneumonia; Merkel (22) in empyema and pericarditis; Von Gunz (23) in scarlet fever; Lebert (24) in pneumonia and double pleurisy; Guttman (25) in pleurisy, the old ulcer which was adherent to the diaphragm perforating into the pericardium; Finney (26) in rheumatism and pericarditis, the ulcer perforating into the left ventricle of the heart, which was adherent to the diaphragm; Cade (27) during an eruption of boils; Debove (28) in inflammation of the axillary glands; Fitz (29) in follicular tonsillitis; Battams (30) in salpingitis; and many others. There is, therefore, evidence that an infection of the body, sometimes very slight apparently, may cause an originally existing ulcer to spread acutely. I have seen two cases of this nature lately at University College Hospital and they have been already published (31). They were both cases of perforative peritonitis due to chronic ulcer, one gastric, the other duodenal. Both had pyloric stenosis, and both commenced bleeding a few days after the operation for perforation.

The autopsies showed that in the former case an acute extension of the original ulcer had occurred in the mucous membrane, producing a triangular area extending from the ulcer, and denuded of its mucous membrane; and that in the latter case an acute ulceration had commenced in the edge of a gastric ulcer involving the cardiac orifice, and had extended up the whole circumference of the oesophagus for a distance of about four inches. I have already said that these cases had pyloric obstruction. That pyloric obstruction alone, in the absence of a general infection of the body, is sometimes able to cause an already existing ulcer to extend acutely I have shown experimentally (32), and there is no doubt that it played a part in the above cases as the pyloric stenosis was unavoidably produced at the operations.

3. An ulcer of the stomach may first declare its presence by symptoms some weeks or months after an infection which is known to be able to give rise to acute ulcer. Such ulcers have been found at operation or after death, and have had clinical histories and post-mortem appearances absolutely like those of simple ulcer of the stomach as seen in medical practice in which no definite sign or history of infection can be obtained.

Such cases have been described as occurring after infective diseases by Cazeneuve (33), Codivilla (34), Mikulicz (35), Régnier (36), Morot (37): after metritis and peritonitis by Bucquoy (38): after dysentery by Bourcy (39). Cases of haematemesis occurring several weeks or months after a local or general infection have also been recorded by Letulle (40), Fabriès (41), and many other observers. A case of this description¹ occurred at University College Hospital in 1910, seven months after operation for perforation of the appendix in which general peritonitis was present and which was followed by the formation of local abscesses.

¹ *Hospital Register*, No. 527. Dr. Risien Russell.

Ulcers have been found in the stomach or duodenum several weeks after the occurrence of burns, by Cooper (42), Wilks (43), Keate (44), Mayo Robson (45), and others. The specimen from the case described by Cooper is at present in the museum at University College Hospital Medical School (*Surgical Catalogue*, No. 1582). It consists of a thickened ulcer adherent to the pancreas, which is exposed in its base.

It must be admitted that the above observations lend some support to the view of the acute origin of chronic ulcer of the stomach.

Many ideas have been formed with regard to the nature of the initial lesion which gives rise to chronic gastric ulcer, and much experimental work has been undertaken with the object of producing ulcer of the stomach. In all cases the supposed or experimentally produced initial lesion has really involved an acute process. In the human subject such lesions are the actual causes of acute ulcer, and they result in the production of acute ulcer in animals.

The pathology of chronic ulcer of the stomach is closely bound up with several different processes, and in studying this subject it is essential to distinguish between these processes, and to study them separately, a mode of procedure which has not hitherto been adopted.

Thus the acute process by which the initial loss of substance is formed is essentially different from the chronic process which leads to thickening of the acute ulcer and transforms it into a chronic ulcer. The process by which both the acute and chronic ulcers spread occurs with varying degrees of acuteness, and the precise factors taking part in this process may be the same as, or different from, those involved in the process of production of the initial lesion. Again, the factors causing an arrest or a delay in the healing of the ulcer require a separate consideration. This communication is especially concerned with the *mode of spread and the early thickening of acute ulcer*, and an attempt will be made to show in what manner this lesion is transformed into a chronic ulcer. In the cases described I am unable to say what was the initial lesion, and that part of the subject is beyond the scope of this paper. It will, however, be of advantage if a definite idea of what is implied by the term 'acute ulcer' is first given, because the term 'erosion' has crept into common use and is applied in different senses by different writers.

DEFINITION.

Cruveilhier (46) in 1821 was the first observer to describe 'erosions or haemorrhagic ulcerations', by which term he meant losses of substance resulting from localized haemorrhage into the mucous membrane, and considered that they commenced in the capillary network. He also calls superficial ulcers beginning in other ways 'erosions'. Rokitansky (47), writing at a later date, likewise uses the term in its wider sense, and thinks that 'haemorrhagic erosions' occasionally arise in the glands of the mucous membrane.

At the present time some authorities apply the term 'erosion' indiscriminately

to any acute loss of substance, whether it penetrates deeper than the mucous membrane or not, whilst others limit it to lesions involving the superficial portion of the mucous membrane.

Others, again, distinguish it definitely from ulcer and confer upon it the dignity of a special disease. Irrespective of the origin of the disease the term 'haemorrhagic erosion' is frequently applied to follicular ulcers and ulcers of necrotic origin; thus the 'exulceratio simplex' of Dieulafoy, which is probably a follicular ulcer, is often called 'haemorrhagic erosion', and the same lesion when it reaches the peritoneum is called 'acute perforating ulcer'.

For the further advance of knowledge in the pathology of gastric ulcer it is essential, therefore, that a more precise nomenclature should be adopted.

I have pointed out elsewhere (48) that *from the point of view of morbid anatomy* an 'erosion' must be regarded as a superficial ulcer, and that when once formed there can hardly be a clear distinction between them. Each of the initial lesions mentioned below may give rise to a superficial or deep ulcer, so that if we wish to distinguish definitely between an 'ulcer' and an 'erosion' the latter term should not be applied to a superficial ulcer. *From the point of view of general pathology* or the process of formation we can, however, distinguish between an erosion and an ulcer. In infective disease, purpuric conditions, and severe anaemias, profuse haemorrhage may occur from the mucous membrane of the stomach in the absence of any ulcer whatever. In such cases it is not uncommon to find at the autopsy superficial erosions having the appearance as if the superficial layers of the mucous membrane had been lightly rubbed off with the finger. These erosions are *mechanically* produced by the escape of blood from the surface and are comparable to abrasions and injuries of the surface which heal rapidly, have no tendency to spread, and cannot be called ulcers; they are in fact 'haemorrhagic erosions'. In the conditions of gastritis and passive congestion of the stomach bleeding may occur from the mucous membrane, the blood escaping from the enlarged capillaries and breaking through the surface of the mucous membrane, thereby producing 'erosions'. It is more useful, in my opinion, to reserve the term 'erosion' entirely for this condition and definitely to distinguish it from 'ulcer', which is *produced by the gastric juice acting upon a damaged portion of the mucous membrane*, and which may involve the mucous membrane only or penetrate to the peritoneum.

FORMATION OF ACUTE ULCER.

Our knowledge of the processes leading to the formation of the initial loss of substance in the mucous membrane is very deficient, because opportunities for the post-mortem examination of specimens are not frequent.

We *do* know, however, that in the human subject such losses of substance arise chiefly in three ways: (1) by necrosis of a localized portion of the mucous membrane; (2) by a localized interstitial haemorrhage into the mucous

membrane; (3) by inflammation and softening of a lymphoid follicle of the mucous membrane.

All these processes are acute, and result in the death of the tissue affected, or so damage it that it falls an easy prey to the action of the gastric juice. In either case the gastric juice acts equally rapidly and the tissue is speedily removed. In my own experiments (49), when the gastric cells were exposed to the action of gastrotxin the gastric juice produced necrosis in a few hours and the whole tissue was removed within twenty-four or forty-eight hours. The same feature is observed in the human subject in the case of acute gastric ulcer resulting from burns and infective disease. When once the dead tissue is removed an acute ulcer results, and, unless the ulcer is incompletely formed, or other lesions which have not yet developed into ulcers exist, it is quite impossible to say from an examination of the specimen in what manner the ulcer took its origin. It is quite true that haemorrhages into the mucous membrane may assume the form of long black streaks or irregular blotches, and that the ulcers resulting from them may be of a similar irregular shape; and also that follicular ulcers are often tiny and scattered throughout the surface of the stomach. But typical round ulcers, few in number or single, may and commonly do result from an interstitial haemorrhage or an inflamed follicle. It is probable that acute ulcer may have other origins of which we are at present ignorant, so that judged from the standpoint of general pathology there are several varieties of acute ulcer, whilst from that of morbid anatomy we are unable in most cases to recognize these varieties. It is probable that any variety of acute ulcer is capable under suitable conditions of undergoing the changes to be described later and developing into chronic ulcer, but in the present state of our knowledge it is not permissible to say which kind of ulcer most commonly undergoes such changes or whether there is any variety of ulcer which invariably does not.

THE FATE OF THE ACUTE ULCER.

1. *Normal Healing.*

In the majority of cases an acute ulcer commences to heal at once, and the process of cicatrization is completed in so far as the scar is covered with rudimentary mucous membrane in three or four weeks according to the size of the ulcer.

This is proved by experiments upon animals, in which acute ulcers, however produced, conform to the above rule. It is also proved in the human being by the healing of injuries inflicted upon the stomach, by the number of scars found after death, and by direct observation. The number of scars found after death is known to be considerable, but the statistics compiled by various observers deal chiefly with chronic ulcer, and it is in connexion with the acute variety that I am now speaking. The scars of acute ulcers are very often missed unless some special method of observation is practised (50). Clinically, acute ulcer of the stomach occurs in three chief types of cases: (1) acute infections and intoxica-

tions, (2) chronic infections, (3) simple acute ulcer as commonly met with in medical practice, which is found either in association with some other disease, with which it may or may not have any connexion, or in the absence of any other obvious disease or infection of the body. Even in regard to this third class evidence is accumulating which shows that, at all events in some of the cases, an unsuspected focus of infection, as for instance chronic appendicitis, may be the cause of the ulcer.

Of 100 cases of acute ulcer occurring in various infective processes, the literature of which I have examined, in 39 one ulcer only was present, and in 61 the ulcers were multiple.

In the acute infective cases all the ulcers are in an open condition and scars of acute ulcers are only rarely seen (51), whilst in the chronic infective cases it is not uncommon to find partially healed ulcers and scars together with recent ulcers in the same stomach (52). In the third class I have found that scars together with open ulcers are found in more than half the cases. The patients belonging to this class do not often die, and the available material is small, so that I have only been able personally to examine thirteen cases. Of these thirteen cases, counting both scars and ulcers, in five there was a single lesion, and in eight multiple lesions were present, giving percentages of $38\frac{1}{2}$ and $61\frac{1}{2}$ respectively. These numbers agree closely with the percentages given above for the infective cases, but in this case the multiplicity is chiefly due to the number of scars present. Thus, in six of the thirteen cases there were ulcers only, in five of which the ulcer was single and in one of which multiple ulcers were present. In the remaining seven cases there were ulcers and scars, in five of which the ulcer was single and in two multiple ulcers were present, the scars being single in three instances and multiple scars being present in four. So that a single ulcer was present in ten out of thirteen cases, or in about 77 per cent. On the other hand, in the seven cases with scars, the latter were multiple in four instances, or in about 57 per cent. A single ulcer is also more likely to be found than multiple ulcers, whether scars are present or not.

In no case were there more than six lesions present in the same stomach, whilst in the infective cases several hundreds may occasionally be present, although even in these cases there are usually no more than from two to eight.

These numbers are very small and only provisional conclusions can, therefore, be drawn from them, but it appears that the longer the patient is likely to live, the more likely are scars to be found in the stomach after death, whether the ulcers are of infective origin or not.

Not only does acute gastric ulcer very commonly heal, but it tends to recur in the same individual, because it is unlikely that the multiple scars found in more than half the cases were all the result of ulcers produced at the same time, since a single open ulcer is found in 77 per cent. of cases.

Direct observation also confirms the view that acute ulcer readily heals. During the formation of an acute ulcer it is not uncommon for an artery in the submucous coat of the stomach to be opened up. In such cases it sometimes

happens that the patient dies, although such an event only very rarely occurs at once.

It is the repeated haemorrhage which kills the patient, so that death is usually delayed for a longer or shorter time. At the autopsy in such cases, as I pointed out in a previous paper (53), the edges of the ulcer usually show distinct signs of healing. In fact the base of the ulcer may be almost entirely covered with epithelium up to the open mouth of the artery, which then appears as a hollow projection in the centre of a scar, from which blood can be squeezed.

In spite of the condition of anaemia of the patient the ulcer has rapidly healed. Such a lesion is very difficult to find even after the stomach is removed from the body and washed.

It may, therefore, be taken as proved that acute ulcer of the stomach in man usually heals rapidly, and confirmation of this statement is afforded by the fact that acute ulcer in animals, however produced, likewise heals rapidly.

2. *Delayed Healing.*

Experiments upon animals, in which an acute lesion of the gastric mucous membrane has been produced and in which subsequent procedures have been adopted to prevent the healing of the lesion, have not resulted in the production of a chronic ulcer but have merely caused a delay in the healing. My own experiments (54) in this connexion have shown that retention of food in the stomach, either due to the character of the food itself or to a condition of muscular insufficiency of the stomach, is an important cause of the delay in the healing of an acute ulcer. In such a case the base of the ulcer is liable to become necrotic from the prolonged action of the gastric juice, or to be excessively fibrous, so that the epithelium grows over the base with greater difficulty and the newly-formed mucous membrane is not so perfectly regenerated. It is, therefore, to be expected that a similar condition prevails in the human subject, and in 1910 (55) I published a very typical instance of this. Such cases cannot be rare, but are only to be recognized by careful examination. The patients are not very likely to die, because they have got over the initial stage of acute ulcer, which is the most precarious time. This type of ulcer can be recognized by the following points, and in these points it absolutely corresponds with similar ulcers in animals. The ulcer is of small size and corresponds in dimensions with the original extent of the lesion, which can easily be gauged, because the muscularis mucosae is not re-formed during healing and regenerated mucous membrane can be distinguished microscopically from normal mucous membrane. There is more thickening of the base, whether the muscular coat had been originally perforated or not, than occurs in the condition of normal healing, and more scarring of the wall of the stomach results. If regeneration of the mucous membrane has barely commenced, the edge of the ulcer ends abruptly and is smooth and rounded, so that the ulcer appears to be punched out. The edge will, however, be found to

slope if the epithelium has commenced to grow over the base. The base is smooth and has grown up more or less level with the mucous membrane. The ulcer may be contracted to an oblong or oval form and the surrounding mucous membrane more or less thrown into radiating folds and lines, owing to shrinkage of the fibrous tissue in the base.

The clinical history of such a case may indicate the age of the ulcer, but only reliably if an attack of haemorrhage has coincided with the formation of the acute ulcer, so that the period at which the latter appeared can be decided.

What proportion of chronic ulcers results from the mere arrest of healing of an acute ulcer it is impossible to say. Not many, I think, because in the vast majority of chronic ulcers which I have examined there is evidence that the ulcer has been spreading.

It is quite true that now and then one meets with small chronic ulcers with thickened bases in which digestion is apparently going on, although there is no progressive lateral extension; but most of these ulcers have been extending for a certain time, the process of extension has been arrested, and the small size of the ulcer is due to contraction of the fibrous base.

3. *Extension of Acute Ulcer.*

In an acute ulcer which is extending two processes are to be recognized: a destructive process by which the ulcer increases in size, and a secondary inflammatory process by which it becomes thickened and acquires the property of chronicity.

An acute ulcer spreads in two directions, *laterally* by extension in the mucous membrane and also *in its depth*. The resulting shape depends upon the relative amount and rapidity of extension in each direction, and upon the degree of inflammatory thickening which has taken place. It may be spreading laterally in *each* direction, but sooner or later its extension in one or more directions comes to an end, so that whilst one edge remains stationary another may be extending. The lateral extension entirely depends upon destruction of the mucous membrane.

Extension in the depth of the ulcer depends upon digestion of the walls of the stomach forming the base of the ulcer, and of the inflammatory tissue which has been secondarily formed. If the lateral extension occurs equally in each direction, the ulcer will be round; if in one direction more rapidly than in the other, it will be oblong or more irregular in shape. The same result is brought about by the arrest of extension of some particular edge. Two ulcers may meet and join together during their lateral extension, also giving rise to an irregular shape, the line of junction being marked for some time by an elevation in the floor of the resulting ulcer.

In an actively extending acute ulcer the mucous membrane is destroyed first and the edge of this appears to be sharply punched out.

Internal to this edge of mucous membrane is to be seen a thin ring of submucous tissue about to be destroyed, whilst the base of the ulcer is formed of muscular tissue, which is most excavated in the centre, as this portion has been exposed longest to the action of the gastric juice. At a further stage the excavated portion of muscle in the centre becomes perforated and the sub-peritoneal tissue exposed. Unless this latter structure has already become thickened the peritoneum may necrose and perforation occur or adhesions form. Inflammatory thickening and adhesions of the omentum are commonly present although the ulcer has not perforated. Two or three weeks are quite a sufficient time for such adhesions to form. The sides of an acute extending ulcer are, therefore, terraced and the cavity funnel-shaped and deepest in the centre. The more rapidly it has extended laterally the more sloping will be the edges of the cone and the more shallow will it appear, the base being in such cases not thickened to the naked eye (Figs. 1, 7). If it has extended slowly there is more time for inflammatory thickening to have taken place and the result will be a deep cone-shaped cavity.

One edge, which has extended more rapidly in the superficial direction than the other, will be more sloping, and the apex of the cone then becomes eccentric. Such an ulcer may stop extending laterally, but show no tendency to heal. Digestion, however, of the base of the ulcer still goes on more or less slowly and small sloughs separate from the sides, so that the mucous membrane at the edge becomes overhanging and undermined and the cavity more globular in shape (Fig. 6). The base of such an ulcer is formed of thickened peritoneum or inflamed omentum, or it has become adherent to an organ or tissue which offers considerable resistance to the action of the gastric juice. If not, perforation sooner or later occurs, but thickened peritoneum seems to offer a considerable resistance to digestion. The perforation occurs by a portion of the peritoneum becoming necrotic and giving way, the ragged aperture soon being converted into a smooth round hole. Such ulcers are usually described as chronic, and they are certainly on the way to becoming chronic, but these cases of which I speak have a short history, and my experiments on animals have demonstrated that quite a considerable amount of thickening may occur in a few weeks. The other class of case in which extension has occurred rapidly in a lateral direction is perhaps more interesting still. In these cases the ulcer is quite shallow and the thickening is inappreciable, except at the part which has been longest formed.

If the ulcer be extending equally in all directions the mucous membrane is sharply punched out all round and surrounds a narrow ring of submucous tissue (Fig. 1). The base is formed of muscular tissue alone or with subperitoneal tissue and fat showing through in the centre. Such an ulcer may be as large or larger than a shilling. A more interesting condition, and one which closely simulates a chronic ulcer, is that in which one edge of such an ulcer has stopped extending laterally. This edge becomes overhanging by separation of sloughs of the underlying stomach wall and is more or less thickened and raised (Fig. 4). The other edges are terraced with the mucous membrane sharply punched out, the sides

sloping more or less obliquely in proportion to the acuteness of the process of lateral extension. Sometimes at one spot the mucous membrane is extensively destroyed, laying bare a large tract of submucous tissue, whilst internal to this the muscular coat is also extensively visible, the side sloping very gradually indeed towards the base. At such a spot extension is much more rapid than at another where the edge slopes more abruptly. This must be carefully distinguished from the condition of commencing cicatrization.

A healing edge is not terraced. The base at this spot is smooth and slopes away towards the centre, and the mucous membrane becomes thin and gradually lost on the surface of the granulation tissue (Fig. 8). The base of such an extensive ulcer is formed of peritoneum slightly if at all thickened, although the omentum externally is inflamed and matted. Large vessels commonly ramify in the base and very often one or more are opened and present bleeding-points. Perforation may have occurred at one spot.

The blood-vessels offer a considerable resistance to digestion. They are sometimes cleanly dissected out and occasionally may be seen running for some distance along the edge of the ulcer.

Broadly speaking, this shallow type of ulcer appears to be commonly situated on the small curvature of the stomach or near it, whilst the funnel-shaped ulcer, which is smaller and tends to perforate, is more commonly situated on the anterior or posterior wall, where the blood-vessels are not so large. The fact that a *chronic* ulcer on the small curvature is most likely to bleed, whilst a similar ulcer on one of the surfaces is most likely to perforate, is a fact well known. I particularly wish to emphasize the similarity in the case of acute spreading ulcer. I do not intend entering into any discussion with regard to the factors influencing the rapidity and mode of spread of the ulcer, or the occurrence of the secondary inflammatory process, because the facts at hand concerning these processes are at present too ill defined, and in this paper I merely wish to demonstrate the fact that acute ulcer extends, thickens, and becomes chronic, and also the morbid anatomy of the conditions produced.

The microscopical examination of these cases is very interesting because it shows the transition from acute to chronic ulcer in a striking fashion. In all cases the mucous membrane at the edge of the ulcer and for some distance around shows the changes characteristic of gastritis. The whole mucous membrane of the stomach may show such a condition, but in other cases the inflammation is limited to a small region surrounding the ulcer.

I have already mentioned that gastritis with inflammation of the lymphatic follicles is one cause of acute ulcer of the stomach, and it is not surprising, therefore, that an acute spreading ulcer should be found in a stomach the subject of a generalized gastritis. But in those cases in which the inflammation is limited to the region of the ulcer there is no reason to believe that this inflammation is of a different nature from that which affects the other coats of the stomach—namely, that it is a secondary condition to the presence of the ulcer. I shall not attempt fully to interpret all the changes in the mucous membrane in

this communication, because they are of a very complicated nature, and the material I have had to work with is not enough from which to draw many general conclusions. I will merely mention that in one case the more rapidly spreading edge, with widespread destruction of the mucous membrane, was affected with a more intense form of gastritis than that affecting the more slowly spreading edge. Whether this indicates any definite relation between the condition of the mucous membrane with regard to inflammation and its digestion by the gastric juice must be left for future observations to decide, especially in view of the fact that the presence of gastritis is no impediment to healing. The cells of the inflamed mucous membrane proliferate readily, and, in those cases which are healing, cover the granulation tissue of the base rapidly, growing down into the cellular stroma in the form of glands. So that one may see at the edge of the ulcer original glands embedded in the cellular stroma and dilated into cysts, newly-formed glands between them, and newly-formed epithelium covering the surface. The appearances presented by the proliferation of this inflamed mucous membrane are extremely difficult to interpret, and it sometimes seems as if the newly-formed mucous membrane itself became inflamed and that many of the glandular mucous cysts were of new formation. It is difficult to draw a hard and fast line between the newly-formed stroma in which the young glands are proliferating and the inflammatory stroma occurring between the original glands as the result of irritation.

At the *spreading edge* of an acute ulcer the submucous tissue is seen to be slightly thickened and the muscularis mucosae by this means elevated from the underlying muscular coat for a short distance. It is finely fibrous, and infiltrated more or less with round cells, especially under the muscularis mucosae. The coats of the vessels embedded in it may be thickened. On the one hand it rapidly passes into the normal submucous tissue at a short distance from the edge, and on the other into the base of the ulcer, where it has the same characters as at the edge, is thickened, fuses with the muscularis mucosae, and forms the peripheral part of the floor of the ulcer. Patches of necrosis can be seen in the superficial layers at its inner edge, by the separations of which it disappears, laying bare the muscular coat or subperitoneal tissue in the centre of the base of the ulcer (Fig. 2). The bundles of muscular tissue have between them an infiltration of cells, and the peritoneum may be microscopically thickened also. The muscularis mucosae at the edge of the ulcer is thicker and more indistinct than normal, and gradually blends with the submucous tissue at the edge of the ulcer.

The thickening of the submucous tissue is an important condition, because it constitutes the first stage in the thickening of the edge of the ulcer, which gives it the character of chronicity. The submucous thickening is more marked than that in the other layers, and this fact also applies to chronic ulcer, in which it has been recognized for some years (Fig. 11). In cases in which the mucous membrane is being rapidly destroyed the submucous tissue is not thickened immediately under the mucous membrane, but only in the base of the ulcer, the

inflammatory thickening in its formation not being able to keep pace altogether with the destruction of the overlying mucous membrane.

The mucous membrane of the edge, as I have already mentioned, shows varying degrees of gastritis. There is a considerable degree of round-celled infiltration, and towards the edge of the ulcer the glands become shorter and fall over towards the base, sometimes lying almost parallel with its surface. The cells in the tubes tend to desquamate, and at the extreme edge the mucous membrane is composed merely of strands of interstitial tissue, with rows of desquamated gland cells between them; it is necrotic on the surface and infiltrated with round cells. The lymphoid follicles in the immediate vicinity are enlarged, spread out, and become insensibly continuous with the round-celled infiltration. Sometimes the glands have mostly disappeared for a little distance beyond the edge, the surface of the mucous membrane being very uneven and necrotic and the tissue chiefly consisting of round cells, strands of interstitial tissue, and a few groups of gland cells in places, the whole thickness being much less than that of the normal mucous membrane.

The examination of an *edge which has stopped extending* shows that the submucous tissue is very considerably thickened, and that this thickening extends for some distance from the edge, where it gradually thins and fades imperceptibly into the normal submucous tissue. It has, therefore, the appearance of a wedge, the base of which forms the side of the ulcer and raises up the mucous membrane separating it from the muscular coat (Figs. 3, 4, and 6). It consists of a fibro-cellular material which is fairly vascular, the vessels of which are a little thickened. The free end of this thickened submucous tissue is necrotic and gradually disappears, undermining the mucous membrane, whose free edge, therefore, may bend slightly down towards the base of the ulcer and appear somewhat retracted.

There is no doubt that when the muscular coat is perforated in acute ulcer, its retraction turns in the edge of the mucous membrane; but this bending down of which I am speaking is not due to muscular retraction, it is due to undermining of the mucous membrane by digestion of the thickened submucous tissue. Sometimes the deeper portion of the submucous tissue has completely disappeared, with the result that the mucous membrane at the edge has collapsed on to the muscular coat, a narrow cleft extending in between the two.

At some distance from the edge of the ulcer there is commencing infiltration of the muscular coat with cells, and the muscle fibres are degenerating. This condition increases towards the edge and the infiltration becomes continuous with, and of the same nature as, the submucous tissue.

Bundles of muscle fibres can still be recognized at the edge of the ulcer, embedded in the fibro-cellular tissue which extends through them from submucous to subperitoneal tissue, which, together with the peritoneum, is also thickened. The free ends of the muscle fibres become necrotic in the same manner as the submucous tissue and separate as sloughs. In this way the previously terraced edge of the ulcer becomes thicker and undermined, the change being brought about

by a secondary inflammation, which spreads outwards into the wall of the stomach, and by digestion of the exposed parts of the sides and base of the ulcer. The base of the ulcer eventually becomes formed of subperitoneal tissue infiltrated with cells and thickened, the superficial strata being necrotic in a thin layer. In places masses of fat can be seen projecting into the floor of the ulcer. The walls of the vessels embedded in the fibrous tissue are thickened secondarily.

The mucous membrane at such a point is of normal depth almost to the extreme edge. The glands are well formed, often dilated and transformed into mucous cysts, the cells being flattened out, and infiltrated with round cells to varying extents. At the extreme edge the glands become rapidly short and bend over towards the base of the ulcer. There is here considerable interstitial fibrosis and the mucous membrane commonly ends by fusing firmly with the superficial layer of the submucous tissue, forming a smooth edge. The muscularis mucosae broadens out towards the edge, becomes cut up by round cells, and the muscle cells degenerate and blend with the submucous tissue. The whole edge of the ulcer may have this appearance, or only one side, whilst extension is going on in the other directions with varying degrees of acuteness. All these steps may be found in the same ulcer, and ulcers in this condition may be present in the same stomach with more recent ones in which the process is just commencing.

In those cases in which the whole ulcer is healing, the changes are very similar to those which occur in the healing of acute ulcer in animals, the only difference lying in the fact that the mucous membrane is inflamed in the former.

I was able to show experimentally (56) that the chief obstacle to healing lies in the condition of the base of the ulcer, not in the overgrowing epithelium, and so it is in these cases, for when once extension of the ulcer has stopped, although gastritis is present, the epithelium readily proliferates and, if the necrotic portions of the base have separated and the latter has become covered with granulation tissue, grows over the base in a single layer to develop later into glands as is usual in healing. The granulation tissue does not always grow up level with the mucous membrane, but the latter accommodates itself to the resulting depression as in animals. The amount of contraction of the stomach wall depends upon the extent of the ulcer both laterally and in the depth. When the peritoneum has been exposed the cicatrix extends throughout the thickness of the wall of the stomach.

4. *Clinical History.*

The following table gives the analysis of the clinical symptoms of the cases described in this paper:

Case 1. F.; aged 53. Indigestion absent. Pain absent. Vomiting uraemic. Rigidity absent. Tenderness absent. Bleeding present. Perforation absent. Condition of ulcer: Cardiac half of small curvature and posterior wall (pyloric). Rapidly spreading. Slight thickening commencing.

Case 2. F.; aged 60. **Indigestion** absent (?). **Pain** absent before perforation. **Vomiting** absent before perforation. **Rigidity** presumably absent before perforation. **Tenderness** presumably absent before perforation. **Bleeding** five years before. **Perforation** present. **Condition of ulcer**: Anterior wall (centre). Slowly spreading and healing. Slight thickening. Scars of old acute ulcers.

Case 3. F.; aged 17. **Indigestion**: Discomfort after meals for 'some time'. **Pain** absent before perforation. **Vomiting** absent before perforation. **Rigidity** presumably absent before perforation. **Tenderness** presumably absent before perforation. **Bleeding** absent. **Perforation** present. **Condition of ulcer**: Anterior wall (cardiac). Rapidly spreading. Very slight thickening. Scars of old acute ulcers.

Case 4. M.; aged 51. **Indigestion** absent. **Pain** lower abdomen, one month. Not related to meals. **Vomiting** commenced after the pain. **Rigidity**: Whole abdomen. **Tenderness** general, and especially in both iliac fossae. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Small curvature (about centre). Healing. Some thickening of edges and base.

Case 5. M.; aged 42. **Indigestion** for years. Aching pain on and off in epigastrium two hours after meals. **Pain** severe for one year. Independent of food also. **Vomited** frequently after food. **Rigidity**: Upper recti both sides. **Tenderness**: Left costal margin. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Small curvature $1\frac{1}{2}$ in. from pylorus. Advanced in healing; some thickening.

Case 6. M.; aged 37. **Indigestion** two years. Slight pain in epigastrium and back one and a half hours after food. Acid and gaseous eructations. Relieved by food. Wasting. **Pain** severe for one month. **Nausea and vomiting** half an hour after meals for three months; relieved the symptoms. **Rigidity** absent. **Tenderness**: Mid-line half-way between ensiform and umbilicus and right iliac fossa. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Stomach dilated. Ulcer on posterior wall near pylorus. Advanced in healing; some thickening.

Case 7. M.; aged 53. **Indigestion** six to seven months. Slight pain or distension, and fullness in epigastrium one and a half to two hours after meals. Not relieved by food. Acid eructations. **Severe pain** seven days, epigastrium and along costal margins, two to two and a half hours after food. **Vomiting** seven days; after food; relieved pain. **Rigidity** slight, of upper recti. **Tenderness**: Centre of epigastrium. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Stomach dilated owing to kinking of pylorus. Ulcer on small curvature $1\frac{1}{4}$ in. from pylorus; spreading; some thickening.

Case 8. M.; aged 50. **Indigestion** as long as he could remember. Wasting five months. **Severe pains** five months in upper part of abdomen, more or less constant and increased by food. **Vomiting** absent. **Rigidity**: Upper recti. **Tenderness** midway between ensiform and umbilicus. **Bleeding** present. **Perforation** absent. **Condition of ulcer**: Almost whole of small curvature. Marked thickening all round. Base formed by pancreas partly. Spreading.

It is not justifiable to draw general conclusions with regard to such variable quantities as symptoms from a small number of cases, but there are one or two points of interest which appear to be established by a perusal of the table. Broadly speaking, it appears that the more recent the ulcer is, the more nearly the symptoms approximate to those of acute ulcer, whilst the older and the more thickened it is, although healing may be advanced, the more like those of chronic ulcer are its clinical manifestations. Such a conclusion seems self-evident, but it is very interesting and important that it should be shown in a series of cases known to be transitional between acute and chronic ulcer. The diagnosis of acute from chronic ulcer is extremely difficult and is only to be made in certain cases. This latter point is not surprising when it is borne in mind that all transitions as shown by these cases may exist between the two

conditions. The presence of an acute ulcer in the stomach is not necessarily associated with symptoms; in fact, it is probably the case that most acute ulcers give rise to no direct symptoms. This is certainly true in the ulcers of infective conditions. The stomach may be riddled with ulcers, and yet the patient may complain of no symptoms. There is no reason to suppose that acute simple ulcers, as commonly occurring in medical practice and in which there is no obvious infection of the body, are exceptions to this rule. My own experience in this respect entirely agrees with that of other observers. In the majority of cases the first symptom to attract attention is sudden haematemesis, and in a very small minority of cases perforation. These conditions are accidental complications of acute ulcer, so that the proportion of acute ulcers in which no symptoms occur must be considerably larger than is ordinarily thought to be the case. Pain of recent origin is only present in a small proportion of cases, and when we consider that those patients who are most liable to acute ulcer are essentially those in which gastric irritability of nervous origin, clinically expressed as pain and vomiting, is especially common, it is probable that pain directly due to the acute ulcer is present in a much smaller proportion of cases. A certain number of the patients have had the symptoms of some form of 'indigestion' for a longer or shorter time before the acute ulcer is recognized. The relation of 'indigestion' to ulcer may be threefold: (1) they may be both the result of a common cause; (2) the acute ulcer of a different origin may have developed in the subject of 'indigestion'; (3) the cause of 'indigestion' may promote the propagation of the ulcer or prevent healing.

The typical history of chronic ulcer is that of long-standing 'indigestion', with pain and vomiting either coming on in attacks with free intervals or continually present. In nearly every case of chronic ulcer pain is present. It is possible that some cases are latent and only announced by haemorrhage or perforation, but such cases are extremely rare. A glance at the list will show that the more acute the ulcer is, the more its symptoms approximate to those of acute ulcer, and the older it is and the more thickening there is present, the more its symptoms are like those of chronic ulcer. The whole question obviously resolves itself into (1) the diagnosis of the presence of ulcer, and (2) the age of that ulcer.

The factor of chronicity is the thickening; hence as soon as thickening has commenced the ulcer is becoming chronic. It is, therefore, impossible to draw a sharp line and to say that at this point the ulcer has become chronic, neither is it possible to recognize such a point clinically. All that it is permissible to say is that in most cases definite pain and other symptoms of ulcer usually only commence when a certain amount of thickening is present, which may not occur until the ulcer has attained considerable dimensions, and that they are more severe and continuous in proportion to the chronicity.

It is frequently difficult to draw a sharp distinction between the epigastric sensations of indigestion and actual pain, and moreover pain may be present in the absence of ulcer, so that there are very real difficulties in the way. But if

the observer has convinced himself that ulcer pain has been present for a few months (five or six for example) he is justified in diagnosing chronic ulcer.

The other symptoms of ulcer depend upon the pain, so that rigidity and tenderness (superficial or deep) are of little help. If the patient be examined when pain is present, or soon after an attack of pain, rigidity and tenderness are likely to be present, but if the examination be conducted when the patient has been free from pain for some time, they will be absent. The pain of a chronic ulcer always disappears with rest in bed and a simple liquid diet, unless some complication is present, and in the history of a chronic ulcer it is not uncommon for the pain to be intermittent, the free intervals amounting to weeks or even months. Whether one ulcer only has been present all the time, or whether more than one, must be judged by the length of time the patient has been absolutely free from pain. It is an exploded idea that the pain in ulcer depends upon irritation of sensory nerves in the floor of the ulcer.

It is undoubtedly a fact that the pain is commoner in proportion to the chronicity of the ulcer, and these cases bear out that statement. If the pain has been present for several weeks, the only pathological condition one can be certain of finding is a certain amount of thickening, but whether the ulcer is spreading or whether it is healing all round or in part is impossible to foretell. The attacks of pain are not related to definite spreading of the ulcer. These cases illustrate a further point of importance, namely, that the presence of haemorrhage, profuse or slight, is no indication that the ulcer will be found to be spreading, because death may occur from the opening up of a vessel in the floor of an ulcer advanced in healing.

So far as they go these cases support the view that the position of the tender point in the epigastrium is no indication of the position of the ulcer in the stomach. I shall return to this point in a future paper in which a series of chronic ulcers will be published.

An important point illustrated by these cases is the remarkable ability to heal which they exhibit, although they have spread to a considerable size and undergone thickening.

There is no need for any special method of treatment. If the patient be put to bed and fed on a graduated diet beginning with milk and raw eggs, in the vast majority of cases the symptoms disappear and healing commences. The more chronic the ulcer the more difficult is the healing process, owing, as I was able to show experimentally and as also demonstrated in these cases, to the condition of the base rather than to a fault in the mucous membrane, which, although in a condition of inflammation, is readily able to grow over the base when it presents a suitable stroma. An objection which has been raised to any close connexion between acute and chronic ulcer is the question of age and sex incidence in the two conditions.

It is considered that since acute ulcer is commonest in young women under thirty years, and that since chronic ulcer is about equal in the two sexes or perhaps a little more common in the male sex after this age, therefore the two

maladies have different origins. It is a matter of common observation that haematemesis due to clinical acute ulcer is commoner in young women than in young men, and this is borne out by post-mortem findings.

Fenwick (57) gives the proportion of female to male between the ages of ten to thirty years as 10 to 1. In the thirteen cases of acute ulcer mentioned above (p. 436) there were three females between 10 and 30 years and no males. Above the age of 30 years, however, there were six females and four males. Clinically speaking, acute ulcer is much less common in females over the age of 30 years than in younger women, so that it appears that haemorrhage from acute ulcer is easily recovered from in early female life, but is a much more fatal event when occurring in a subject of over 30 years of age. It is probably a true statement that simple acute ulcer is commoner in women than in men, that this difference is especially marked under 30 years of age, so that over this age the numbers are much more nearly equal in the two sexes. The fatality from haemorrhage is much greater over the age of 30 years in both sexes than below it. The number of cases of acute spreading ulcer quoted here is only small, but so far as they go they bear out the idea that haemorrhage is particularly fatal in a subject over the age of 30 years, and seem to indicate that there may be more tendency towards spreading and chronicity in the male over 30 years of age. According to Fenwick's statistics (58), of 59 cases of chronic ulcer, 43 were males and 16 females. At the present time acute and chronic ulcer are not separated in most statistics, so that very little information can be gained from them with regard to the occurrence of ulcers in different stages of development in persons of various ages and both sexes. Until the different types of ulcer are separated from each other and new statistics compiled on these lines, we must be content with the statements above.

When one considers that there are different forms of acute ulcer, and that probably some forms have a greater tendency to heal and others to spread; that age and concomitant disease must influence the tendency of ulcer to heal, to spread, and to thicken; that the subjects of ulcer differ individually with regard to condition of digestion and diet; that statistics are largely compiled from clinical material, and that the diagnosis of ulcer is very difficult, statistical objections which are raised to the connexion between acute and chronic ulcer appear to be more imaginary than real.

There is no doubt that such associated diseases as occur in the cases described here, and which have probably no direct connexion in most cases with the ulcer, nevertheless must seriously affect the fatality of the haemorrhage due to the ulcer. The amount and rapidity of formation of the secondary thickening probably depend largely upon the general condition and age of the patient.

CONCLUDING SECTION.

The main object of this paper has been to show how, by the extension of an acute ulcer and the secondary inflammatory thickening which affects the same,

and is a necessary consequence of the unhealed condition of the ulcer, a chronic ulcer arises. The funnel shape of an ulcer is not due to the fact that it arises as a result of vascular occlusion; it is merely the result of the mode of spread of the ulcer. The spread occurs in two directions, laterally and in the depth. If lateral extension has occurred rapidly the funnel is a very shallow one, and this shape disappears when the muscular coat is destroyed, the ulcer assuming a flattened form. If extension has occurred chiefly in the depth the funnel shape is well marked and perforation soon occurs, unless there is a well-marked inflammatory reaction and thickening. Digestion of the sides of the ulcer undermines the edges, so that the flat variety acquires a raised and overhanging edge, and the funnel-shaped ulcer is converted into a globular or other irregular shaped cavity.

Chronic ulcer probably always arises in this manner, because, so far as we know at present, every initial lesion leading to ulcer is essentially acute and produces in the first instance acute ulcer. According to the nature of this initial lesion there are several different types of acute ulcer. They are all under suitable circumstances, very little understood at present, able to spread and become chronic, but there is undoubtedly one particular type of acute ulcer which most frequently undergoes these changes.

Acute ulcer, whatever its origin, tends to heal rapidly and completely within a few weeks, and perhaps there is one type which most commonly does this. Occasionally, without showing any tendency to spread, an acute ulcer may be delayed or arrested in its healing, when thickening occurs and the condition may become chronic.

One sex is more liable to be affected by a particular type of acute ulcer than the other.

The multiplicity or the reverse of the ulcers, the position in the stomach occupied by them, the sex and age of the patient most affected, the recurrence in the same individual, all vary probably according to the type of acute ulcer. For instance, an ulcer due to an acute infective condition is commonly multiple, more often affects the fundus, may occur at any age, does not recur in the same individual, and usually does not spread or become chronic if the patient survives, although there is evidence to show that it may do so. These are the general principles from which the detailed pathology of chronic ulcer must be worked out, and this can only be done by the systematic classification and study of the various forms of acute ulcer.

Finally, I wish to express my sincere thanks to my colleagues on the Medical and Surgical Staff of University College Hospital for their courtesy in allowing me free access to their cases, and for the use of their post-mortem specimens.

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ILLUSTRATIVE CASES.

Case 1.

(Hospital Register No. 1736. Autopsy No. 151. Dr. Sidney Martin.)

L. M., aged 53 years, female, housewife, was admitted to University College Hospital on June 13, 1910. She complained of pain in the head and eyes, giddiness at times, failing vision, wasting, occasional vomiting. These symptoms had been present for six months. She had been constipated for twelve months previously, but had had no other illness, nor had she suffered from indigestion. The heart was hypertrophied, the vessels thickened, and the blood pressure 220 mm. Hg. There was albuminuric retinitis and a variable amount of albumin in the urine. The teeth were in good condition, the upper ones being false. The abdomen was lax, and the right kidney palpable. There was no pain, tenderness, nor any symptom of indigestion. The vomiting occurred at any time, and was not related to food; it continued on and off till the patient's death. She gradually lost flesh, and towards the end of life Cheyne-Stokes respiration developed. On August 9 there was copious haemorrhage from the rectum, the blood being dark in colour, and partially clotted. The patient died the same day.

Autopsy. Red granular kidneys were present. The left ventricle of the heart was markedly hypertrophied and dilated, and the right ventricle was similarly affected, but to a slighter extent. The aorta was atheromatous and the aortic valves slightly thickened. The lungs were emphysematous. There was an old scar at the right apex and a red infarct in the right lower lobe. The liver showed some general fibrosis. The gall-bladder was shrunken and contained six gall-stones. The capsule of the spleen was a little thickened. The intestines contained blood but were otherwise normal. The pancreas was normal.

Stomach (Fig. 1). Two ulcers were present. The larger was situated on the small curvature, which bisected it, at a distance of $1\frac{3}{4}$ inches from the cardiac orifice. Its size was 2 inches by $1\frac{1}{2}$ inches. Its base was formed of sub-peritoneal tissue with muscular tissue in places. At four points were the open mouths of medium-sized branches of the coronary artery. The small omentum was not thickened, nor was the peritoneal base of the ulcer, to the naked eye. The anterior edge was terraced, and sloped very gradually to the base. The mucous membrane had been destroyed over a considerable area, laying bare the

submucous tissue, and internal to this was the muscular coat of the stomach. There was no thickening of this edge. The edge of the ulcer, which was situated on the anterior wall of the stomach, was almost perpendicular, cleanly cut, and slightly raised and thickened, and, as it passed into the edge described above, was terraced. The edge of the ulcer situated on the posterior wall was raised, slightly thickened and undermined, the extreme edge being slightly inverted. The smaller ulcer was $1\frac{1}{2}$ inches by $\frac{1}{2}$ inch in size. It was situated longitudinally in a line with the larger ulcer and posterior to it, but on the posterior wall of the stomach quite close to the small curvature. It was narrow in the centre and evidently formed by two round ulcers which had joined together during their extension. To the naked eye there was no thickening in any part of this ulcer. The mucous membrane was sharply punched out at the edge, and internal to this was a narrow ring of submucous tissue surrounding the whole ulcer. The base was formed of muscular tissue hollowed out in the centre of each original ulcer, and was crossed in the middle by a raised strand of submucous tissue showing where the ulcers had joined. In the centre of the anterior portion of the ulcer was a bleeding-point. The edges of the ulcer all round were terraced, and it had the appearance of being formed by two very shallow funnel-shaped ulcers. By transmitted light the ulcers looked quite thin except along the line where the small omentum was attached to the base of the larger ulcer. There were no other ulcers in the stomach, neither were there any scars.

The microscopical examination of the smaller ulcer (Fig. 2) showed a condition of gastritis affecting the mucous membrane around the ulcer; the round-celled infiltration was only slight, so that the glands were not separated, the lymphoid follicles were a little diffuse, and there was some dilatation of the glands and desquamation of the cells lining them. At the edge of the ulcer the glands were short and bent, and there was necrosis of their superficial ends. The submucous tissue immediately under the edge of the mucous membrane was very slightly thickened, and sloughs were separating from the inner edge of this tissue, gradually exposing the muscular coat in the base. With the exception of some infiltration with cells the remaining coats were not thickened. Sections of the anterior shallow edge of the larger ulcer, where spreading was more rapid, showed a similar condition, but the mucous membrane of the edge and for some distance into the surrounding part was in an advanced stage of disintegration. There was no thickening of the underlying submucous tissue. The thickening of the undermined and raised edge (Fig. 4) was seen to be chiefly due to the increased depth of the submucous tissue, which formed a wedge-shaped mass, the thin edge gradually fading into the normal submucous tissue. The other coats were thickened to a lesser degree. The free edges of the submucous and muscular coats were necrotic, and the undermining was obviously due to separation of this dead tissue. The surface of the base of the ulcer was also necrotic. The mucous membrane at the edge was infiltrated with cells and was not being destroyed, as shown by the fact that the extreme edge of it was fused with the submucous tissue by fibrous tissue. The submucous thickening only extended

out into the wall of the stomach for a short distance. The more perpendicular edge (Fig. 3) of the ulcer showed the same changes, but the undermining had not gone on to such an advanced condition.

Case 2.

(Hospital Register No. 2149. Autopsy No. 122. Mr. Trotter.)

W. A., aged 60 years, female, was admitted to University College Hospital in the evening of August 31, 1909. She was suffering from general peritonitis, and was considered to be in too bad a condition for operation. She died the same evening. She was a cook in a private house, and so far as was known had been perfectly well and not complained of indigestion; in fact, she had cooked the dinner on the evening of August 30, and shortly afterwards was taken with a sudden severe pain in the abdomen. Five years previously she had suffered from a violent attack of haematemesis.

Autopsy. The body was stout. Mitral stenosis was present, the orifice admitting the tip of one finger, the right side of the heart and the left auricle being hypertrophied and dilated. There were some recent vegetations along the free edge of the agglutinated mitral valves. There was brown atrophy of the cardiac muscle and atheroma at the base of the aorta and of the coronary arteries. There was also atheroma of the abdominal aorta. The pericardium contained an ounce of clear fluid. The lungs were emphysematous, and the pleurae adherent at both apices. The kidneys were small, the capsules adherent, and there were large areas of atrophy in the cortex of each, which was generally diminished and tough. The renal arteries were thickened. There was general peritonitis, the abdominal cavity containing about three pints of turbid fluid. The stomach and liver were adherent together by recent lymph. The intestines were also adherent. There was a firm and older adhesion between the anterior wall of the stomach, half-way between the pylorus and cardiac end, and the anterior wall of the abdomen. Where this old adhesion was attached to the stomach there were some soft adhesions at one side, which readily gave way, exposing the base of an ulcer (Fig. 5). The ulcer, whose base was thus adherent to the abdominal wall, was about the size of a threepenny piece. One edge was raised and undermined, and the opposite edge sloping and showed signs of cicatrization. The base of the ulcer was hollowed out, and formed of muscular tissue in part and thickened peritoneum covered with black necrotic tissue. The base had probably been torn by the adhesion to the abdominal wall, and the aperture closed by recent adhesions. Two oval ulcers with smooth edges, and whose bases were almost level with the mucous membrane, were situated point to point on the cardiac side of the above-mentioned ulcer, and rather nearer the greater curvature. The mucous membrane around these oval ulcers was puckered and showed lines radiating from them. On the pyloric side of the first ulcer the stomach was a little contracted, and there were signs of several healed superficial ulcers in this position.

The microscopical examination of the raised edge of the first ulcer (Fig. 6) showed considerable thickening of the submucous tissue with necrosis of its free end, giving rise to undermining. This excavation had extended inwards for a considerable distance, and for this reason the mucous membrane was bent down a little towards the base. The superficial muscular coat of the stomach at this point projected beyond the submucous as if it had resisted digestion longer, and there was again undermining below this, separating it from the deeper muscular layer. The mucous membrane showed advanced gastritis with some necrosis of the extreme edge. The shallow edge of the ulcer showed new gastric glands proliferating and growing over a base of fairly dense connective tissue containing some bundles of muscular fibres. At one spot the growth appeared to be delayed by the superficial necrosis of this fibrous tissue. The ulcer had evidently been originally funnel-shaped, and a further excavation of the base had converted it into a rounded cavity, the edge having stopped its lateral extension for some time. The two oval ulcers were almost healed; the mucous membrane was growing over a base of muscular tissue covered by a thin layer of granulation tissue.

Case 3.

(Hospital Register No. 2641. Mr. Raymond Johnson.)

A. M., aged 17 years, female, laundry worker, was admitted to University College Hospital on September 10, 1910. She was suffering from general peritonitis, was operated upon, and died ten days later. Seven days before admission she awoke one morning with a dull pain in the abdomen, which was generally distributed. Two days later she commenced vomiting, but still stuck to her work (mangling). The day before admission she had a hot bath in the morning, and then the pain became more acute, but was still of the same general character. She had previously suffered from 'dyspepsia', which she described as being 'discomfort', in the epigastrium, but there was no vomiting and apparently no actual pain.

Autopsy. Signs of peritonitis were present. The heart, lungs, and other organs showed no disease.

Stomach. The ulcer, which had perforated, was situated on the anterior wall of the stomach, $\frac{1}{2}$ inch from the small curvature, 2 inches from the cardiac orifice, and $4\frac{3}{4}$ inches from the pylorus. It was rounded and shallow. It was about $\frac{3}{4}$ inch by $\frac{5}{8}$ inch in size. The edge situated towards the small curvature was shallow, sloping, and terraced. The mucous membrane was sharply punched out, and internal to this was a shelf of submucous tissue extending for the whole width of the ulcer. Internally again was a ridge of muscular tissue, and the base of the ulcer was formed of thickened peritoneum. The thickening appeared to be chiefly the result of the acute peritonitis resulting from the perforation. There was a large rounded perforation in the base situated nearer the opposite edge of the ulcer, which was slightly undermined (Fig. 7). There was a small

acute ulcer involving the submucous tissue on the posterior wall near the greater curvature at the cardiac end, and near to this the scar of a healed acute ulcer. Another tiny scar was situated on the small curvature at about its centre. A few scattered points of congestion and petechial haemorrhages were situated in the pyloric region on the anterior and posterior wall around the small curvature. Three duodenal ulcers were present—a large one, $\frac{3}{4}$ inch in diameter, reaching to the muscular coat and situated $\frac{1}{4}$ inch from the pylorus on the posterior wall; and two smaller ones about $\frac{3}{4}$ inch further on in the duodenum, one on the anterior, and the other on the posterior wall. They were both smaller than the first one and were healing.

The microscopical examination of the terraced edge showed no thickening of the submucous tissue, nor of the muscular coat, but the peritoneum was thickened in the base. This thickening was apparently due to the recent peritonitis around the perforation. The mucous membrane was very thin, infiltrated with cells, and the glands largely disintegrated. The opposite undermined edge showed considerable thickening of the submucous layer and excavation of the same. The muscular layer projected at the edge and was covered with a layer of necrotic tissue. The peritoneum was considerably thickened, formed the base of the ulcer, and was necrotic on the surface. The mucous membrane showed gastritis, round-celled infiltration, diffusion of the lymph nodules, and dilatation of many gastric glands with desquamation of the cells. This ulcer had the shape of a very shallow funnel. One edge was spreading more rapidly in a lateral direction than the other, with the result that the apex of the funnel was eccentric in situation, and the perforation which occurred at the apex was likewise eccentric.

Case 4.

(Hospital Register No. 2953. Autopsy No. 208. Dr. Sidney Martin.)

J. R., aged 51 years, male, wood-cutter, was admitted to University College Hospital on October 8, 1910. He was complaining of pain in the stomach and of vomiting blood. He was unable to give a very clear account of his illness, but it appeared that the pain commenced in the lower part of the abdomen a month previously, and was not related to meals, but came on irregularly and gradually disappeared. Latterly the pain had become worse, and was continuous throughout the day and night. The bowels were loose to begin with, and later were rather constipated. He began to have a feeling of nausea and to retch, and on October 4 he vomited about a pint of dark thick fluid. The pain continued, and the motions were dark-coloured until admission. He had been in the army five years, and had had enteric fever in India in 1879. He took one to two pints of ale in the day. He had had chronic bronchitis with palpitation and shortness of breath for nine years. On admission he was pale, thin, and breathing rather rapidly. He complained of pain in the lower part of the abdomen. The respiratory movements of the abdomen were rather limited and the whole abdomen was somewhat rigid. There was considerable tenderness on light

pressure, especially in both iliac fossae. No dullness was detected. There was enlargement of the heart and aortic regurgitation. For the next three days the melaena and abdominal pain continued, and then the patient began to improve until October 15, when he collapsed, became very pale, and passed a large quantity of melaena. On the following day he had an attack of haematemesis. The melaena continued, and the patient died on October 20.

Autopsy. The stomach was distended with a large blood-clot and some blood-stained fluid. An almost circular ulcer was situated on the small curvature, which nearly bisected it, the ulcer extending rather farther on the posterior than on the anterior wall (Fig. 8). It was slightly nearer to the cardiac orifice than to the pylorus. Its longer diameter was $1\frac{3}{5}$ inches and its smaller $1\frac{1}{5}$ inches, the latter corresponding almost with the line of the small curvature. The ulcer was quite shallow, the base being formed of fibrous tissue, which apparently was filling up the cavity of the ulcer. There was no more thickening of the base than could be accounted for by the process of healing of the ulcer. The edge of the ulcer which was turned towards the pylorus was slightly overhanging and raised, and that turned towards the cardia was sloping, the mucous membrane gradually fading into the base of the ulcer. The edges were quite smooth and there was no terracing. There was the open mouth of an artery almost in the centre of the ulcer. No other ulcers or scars were present. The intestines and appendix were normal.

The microscopical examination showed that the ulcer was healing all round. Round the edge the base of the ulcer consisted of vascular granulation tissue, and was quite smooth. At the undermined edge a slight cleft was noticeable between the thickened submucous tissue and the free ends of the muscular fibres, and the submucous tissue had been hollowed out. The whole edge was covered and smoothed over with vascular granulation tissue continuous with that of the base. No sloughs nor particles of necrotic tissue could be seen. At the sloping edge the slightly thickened submucous tissue was continuous with, and level with, the granulation tissue of the base. The base of the ulcer consisted of fibrous tissue with vascular granulation tissue superficially, which had grown up during healing and was continuous with the peritoneum. The surrounding mucous membrane was in a condition of marked gastritis. The glands were separated by a cellular stroma, in some places very considerable. The glands themselves were dilated to different degrees, and often completely lined by cubical epithelium containing large accumulations of mucus. In some cases they were very short and many had completely disappeared. There were signs of proliferation of the epithelium, and at the sloping edge the mucous membrane was growing over the base in the fashion quite typical of healing. This case is a very important one, because it represents an acute ulcer which had spread in each direction, the pyloric edge having been the first to stop, and then the usual thickening and undermining occurred. Healing apparently commenced all round after the edges had become clean, and before the cardiac edge had been much thickened and excavated.

Case 5.

(Hospital Register No. 43. Sir John Bradford.)

G. T., aged 42 years, male, outside porter, was admitted to University College Hospital on January 4, 1911. The patient had suffered from indigestion for years. His chief symptom had been a dull aching pain on and off, situated in the mid-line from the lower part of the sternum to the umbilicus. The pain came on about two hours after food, especially tea, and disappeared gradually before the next meal. He was never awakened in the night with pain. For the last year he had never been free from pain for longer than a week at a time, and the pain had been much more severe, and had come on independently of food. He had often vomited after breakfast, but never brought any blood up till January 1. He had been accustomed to drink five or six pints of ale and to smoke $\frac{3}{4}$ oz. of tobacco and ten to twenty cigarettes each day. On January 1, at 8 p.m., the patient suddenly felt ill and vomited up about a pint of dark clots of blood. He had had a meal consisting of tea, toast, and cake two hours previously. The vomiting was repeated on January 3 and 4, but smaller amounts of blood were brought up. On admission the patient was blanched. The abdomen was retracted and the upper parts of the recti rigid on both sides. There was slight tenderness along the left costal margin, but no pain except in the lower part of the abdomen on coughing. On being brought up the lift in the Hospital the patient vomited a clot of blood $3\frac{1}{2}$ by $1\frac{1}{2}$ inches in size. During the next four days blood was passed by the rectum and the patient died on January 8.

Autopsy. A large clot of blood was found, forming a complete cast of the cavity of the stomach. The stomach was distended by the clot, but not otherwise dilated. A round ulcer $\frac{1}{2}$ to $\frac{3}{4}$ inches in diameter was situated on the small curvature, which bisected it, at a distance of $1\frac{1}{2}$ inches from the pylorus. The edges of the ulcer were smooth, not undermined, very slightly raised, and descended abruptly to fuse intimately with the base. The edges were finely puckered and the surrounding mucous membrane thrown into radiating folds. The base was filled up almost level with the mucous membrane, and was formed of granulation tissue. In the centre was a bleeding vessel. The rest of the mucous membrane looked healthy and presented no further ulcers or scars. The small omentum was adherent and thickened. The wall of the stomach at the base of the ulcer was no more thickened than the formation of fibrous tissue during healing would account for. There were no other lesions of importance in the body.

The microscopical examination of the edge of the ulcer showed that the mucous membrane all round was in a condition of gastritis very similar to that of Case 4. The epithelium was rapidly proliferating and a small single layer of cells had grown over on to the base for some distance, forming a thin film (Fig. 9). The base was composed superficially of granulation tissue and in its depth of more dense fibrous tissue continuous with the peritoneum. There was

thickening of the submucous tissue for a little distance out into the stomach, and the other coats were infiltrated with cells. This ulcer had spread for a certain distance all round, and then commenced to heal rapidly, and at the time of examination was in an advanced condition of cicatrization.

Case 6.

(Hospital Register No. 1567. Dr. Risien Russell.)

B. R., aged 37 years, male, tailor, was admitted to University College Hospital on May 28, 1910. The patient had been ill for two years with 'indigestion'. He had had slight pain in the upper part of the abdomen, below the umbilicus, and between the shoulders, which came on $1\frac{1}{2}$ hours after a heavy meal, but not if the patient lived on eggs and fish. The pain came on about every two days and was sometimes absent for a month. He also had eructations of acid fluid and gas, appearing at the same time as the pain. The above symptoms were relieved by food. For the last three months the patient had had nausea and vomiting, which came on especially after the midday meal, and relieved the symptoms. He never vomited blood nor passed black motions. The pain had become much worse during the past month and he had vomited every day about half an hour after food. He had wasted considerably, his appetite was good, and the bowels constipated. The abdomen was lax and its walls thin. Slight tenderness was present on deep palpation in the mid-line half-way between the ensiform cartilage and the umbilicus, and another spot of tenderness was situated midway between the latter and the right anterior superior iliac spine. No tumour was present. The stomach was found to be dilated on physical examination, and a bismuth meal of bread and milk passed out of the organ more slowly than normal, a considerable amount being still present after six hours, showing motor insufficiency of the stomach. Examination of the stomach contents showed a total acidity of 0.3285 per cent., and the total HCl secreted 0.281 per cent. The patient rapidly improved, lost his symptoms, and after the expiration of three weeks a gastro-enterostomy was performed because of the motor delay and dilatation. The patient died the next day, and since a full autopsy was not permitted the cause of death was not known.

Examination of stomach. The stomach was dilated, but there was no stenosis of the pylorus. The duodenum was normal. On the posterior wall of the stomach, about 1 inch from the pylorus, was situated a healing ulcer. It was oval in shape and about $\frac{1}{2}$ in. by $\frac{1}{4}$ in. in size. Its position was transverse, one end being near the small curvature. It was quite shallow, the granulation tissue forming the base being quite clean, and having grown up level with the mucous membrane. The edges of the ulcer all round were sloping and slightly puckered, and the mucous membrane gradually became thinner and thinner as it faded away into the base of the ulcer. The peritoneum corresponding with

the base of the ulcer was opaque and thickened and a few peritoneal adhesions were present.

Microscopical examination. The mucous membrane in the vicinity was thin and showed marked changes of gastritis. At the edge of the ulcer proliferation was taking place, and the epithelium was growing over the base all round the ulcer. The muscular coat had been perforated over a small area in the centre of the ulcer, and the gap was filled up with fibrous tissue continuous with the peritoneum, which was thickened over a somewhat larger area. The submucous coat was much thickened at the edge of the ulcer and for about a quarter of an inch outside this. The base was completely filled up with granulation tissue. The acute ulcer had not spread to any great size, no undermining of the thickened submucosa had occurred, and healing had commenced very promptly.

Case 7.

(Hospital Register No. 3860. Autopsy No. 4. Dr. Risien Russell.)

F. C., aged 53 years, male, violin-maker, was admitted to University College Hospital on December 25, 1910. He had had syphilis twenty years before. He took a pint of beer a day and occasionally spirits. For the past six or seven months the patient had suffered from indigestion. His symptoms were pain, which he said was not severe, and was better described as a feeling of great distension or fullness, most marked in the epigastrium, and which came on $1\frac{1}{2}$ to 2 hours after meals. This feeling used to pass off gradually and was not relieved by taking food. He had acid eructations but no vomiting. His appetite was always good, and he lived on a fairly ordinary diet with perhaps rather less meat than is usually taken. Seven days before admission he commenced to feel definite pain in the epigastrium, which radiated outwards on both sides along the costal margin. This pain was only present after food and came on about 2 to $2\frac{1}{2}$ hours after eating. The pain was relieved by vomiting, which now commenced. On December 20 patient felt faint and brought up about a teacupful of blood brownish in colour. On three later occasions the attack of haematemesis was repeated, the blood being similar in amount and bright red. On admission the patient, a well-nourished man, was pale and restless. His abdomen was somewhat retracted but moved well all over. There was very slight deep tenderness in the centre of the epigastrium, but no superficial hyperaesthesia, and slight rigidity of the upper recti. He continued to pass melaena for the two following days. After this he became delirious and the heart began to fail. His general condition was very bad, and he developed retention of urine and died on January 4, 1911.

Autopsy. The stomach was dilated and distended with gas. It contained a small amount of brownish fluid with small black flakes. On the small curvature, and bisected by it, was a shallow oval ulcer, which extended for about equal distances on the anterior and posterior surfaces of the stomach.

Its long axis was situated transversely. The size of the ulcer was $2\frac{3}{4}$ by $1\frac{1}{2}$ inches and it was situated $1\frac{1}{4}$ inches from the pylorus. There were inflammatory changes in the small omentum, which had contracted adhesions to the gall-bladder and first part of the duodenum. The adhesions were firm, but there was not much thickening. By this means the small curvature of the stomach was somewhat contracted and the pyloric orifice kinked. This had no doubt caused the dilatation of the stomach. The edge of the ulcer turned towards the pylorus was elevated a little and overhanging. It passed gradually into a sloping, almost flat edge, which was turned towards the cardia. The base of the ulcer was not thickened appreciably and was formed of omental and subperitoneal tissue. Around the edge could be seen in places the remains of the muscular coat of the stomach and one part of the sloping edge was definitely terraced. The open orifices of two arteries could be seen in the posterior base of the ulcer. On the posterior wall of the stomach were several superficial ulcers running in a line parallel to the great curvature, their surfaces being black or red. The duodenum was normal. The other organs showed no noteworthy change except some oedema and hyperaemia of the bases of the lungs, and some fatty change in the liver.

Microscopical examination. The raised and undermined edge of the ulcer showed considerable thickening of the submucous tissue, which extended out into the wall of the stomach for some little distance. The muscular coat at this point was about twice its normal thickness, and this thickening was not due to infiltration with cells but to retraction of the muscular fibres. The submucous tissue had been hollowed out into the form of a cleft, and the mucous membrane and underlying submucous tissue had collapsed on to the muscular coat. The peritoneal coat was thickened at this spot. The undermining of the edge was seen to be due to the separation of necrotic portions of the submucous and muscular layers as in the previous cases. There was no attempt at healing and the base was covered with necrotic tissue. The mucous membrane itself showed the changes of gastritis of the same type as Case 4. Sections of the sloping edge showed the mucous membrane in a condition of disintegration. The mucous membrane was thin and infiltrated with cells. The glands were short and often dilated into globular spaces, with disintegration of the epithelium lining them, and in places they had disappeared, although leaving only strands of interstitial tissue with round-celled infiltration and groups of gland cells in places. The submucous tissue was considerably thickened here, and became continuous with the thickened peritoneum, the ends of the muscular fibres losing themselves in the fibrous tissue.

Case 8.

(Hospital Register No. 1312. Autopsy No. 94. Sir Thomas Barlow, Bart.)

This case is one of definite chronic ulcer, and it is introduced here because all the changes which have occurred in it are so precisely like those of the

foregoing cases that it is impossible to believe that it had any other origin than an acute one.

A. L., aged 50 years, male, painter, was admitted to University College Hospital on May 5, 1910. He had suffered from 'indigestion' as long as he could remember, and had had painter's colic two or three times. For the past five months he had had severe pain in the upper part of the abdomen, which was increased by food. He had had no vomiting, but had been wasting and growing weaker during this time. For the last week his motions had been dark in colour. He was in the habit of taking three or four pints of ale a day. On admission he was seen to be extremely pale and wasted. He was constantly wriggling and tossing about in bed and rubbing his legs together, and seemed quite unable to keep still. He also complained very much of feeling cold. It was impossible to obtain any further history from him than the above. The tongue was very dry and the teeth much decayed. There was a slight indication of a blue line on the gums. There was diffuse pulsation over the upper part of the abdomen and tenderness in the epigastrium midway between the umbilicus and ensiform cartilage. Both recti were a little rigid in the upper part. The liver was felt just below the costal margin. On the following day the patient passed some melaena. He remained very restless and slept badly, and on May 9 his breathing became rapid, his heart began to fail, and he died the next morning.

Autopsy. The stomach was dilated. A round ulcer, 2 inches in diameter, was situated on the small curvature which bisected it (Fig. 10). The ulcer extended equally on the anterior and posterior surfaces of the stomach, and was about an inch distant from the pylorus and a similar distance from the cardia, the small curvature being contracted. The ulcer was shallow. The wall of the stomach around the ulcer and extending outwards for 2 inches or more was thickened, stiff, and adherent to the neighbouring structures. The base of the ulcer in places was nodular from the presence of lobules of the pancreas, the surface of which formed the base of the ulcer, and projected into the stomach. The orifices of two small arteries appeared in the base of the ulcer. The small omentum was thickened and adherent, and several enlarged lymphatic glands were found. The edge of the ulcer which was turned to the pylorus was hard and raised. It was also undermined. This undermining of the edge extended round on to the anterior and posterior surfaces of the stomach, and on the anterior surface, especially, large sloughs could be seen to be separating from the edge under the mucous membrane, by the separation of which the latter would become overhanging. The edge of the ulcer turned towards the cardia was very sloping; in fact, the surface of the mucous membrane passed insensibly into that of the base. Sloughs, quite thin and superficial, could be seen separating from the submucous layer internal to the edge of the mucous membrane, and in places at this edge the muscular coat of the stomach appeared on the surface. No other ulcers or scars were to be seen on the mucous membrane. The muscular substance of the heart was pale and soft and showed

areas of marked fatty change, especially in the columnar and papillary muscles. The liver was also a little fatty and the kidneys showed early granular change. The vessels were not thickened. There were no other noteworthy changes to be found in the body.

Microscopical examination. The mucous membrane around the ulcer showed a marked condition of gastritis. The interstitial tissue was densely infiltrated with cells, and the glands were separated to a considerable extent. They were also considerably dilated and many had been destroyed. The submucous tissue was enormously thickened all round the ulcer, and this thickening extended out for about two inches into the surrounding wall of the stomach. The peritoneal coat was also thickened markedly, especially at the edge of the ulcer, but not to the extent seen in the submucous layer. The muscular coat was cut up by, and embedded in the fibrous tissue, but could be recognized up to the edge of the ulcer, and at the sloping edge it came to the surface internal to the thickened submucous layer, the ends of the fibres turning up towards the surface. At the overhanging edge the submucous and other layers forming the side of the ulcer had been excavated by the separation of sloughs, and the mucous membrane at its free edge was turned down and curved backwards so that the extreme edge of the mucous membrane almost touched the base (Fig. 11). This process of excavation could be followed perfectly in places, as large sloughs were actually in process of separation (Fig. 12). Sloughs were also peeling off the submucous layer at the sloping edge. Here the mucous membrane showed both destructive and proliferative changes, and at one spot the epithelium was actually growing up to the edge of a patch of necrosed tissue. The base of the ulcer was formed of dense fibrous tissue, with fat and lobules of the pancreas embedded in it, and there was necrosis of the superficial layers with the separation of tiny sloughs.

DESCRIPTION OF FIGURES.

PLATE 23, FIG. 1. Photograph of the ulcers of Case 1. The lower ulcer is formed of two acute spreading ulcers which have united, the original line of division being represented by a strand of submucous tissue. Each original ulcer is of a very shallow funnel shape. The edge is terraced and the base formed of muscular tissue, hollowed out in the centre. The large upper ulcer shows an acute spreading edge, which is terraced, at the upper left-hand corner. The lower left-hand edge is raised and undermined, and the right edge is almost vertically cut and raised.

FIG. 2. Photograph of a section of the edge of the lower ulcer in Fig. 1. The section shows slight thickening of the submucous tissue of the edge of the ulcer. On the left-hand side of the section a slough is seen to be separating from the submucous tissue. The muscular coat of the stomach is exposed by this means and terracing of the edge of the ulcer produced.

FIG. 3. Photograph of a section of the right edge of the upper ulcer in Fig. 1. The submucous tissue at the edge is considerably thickened and necrotic at its free end. The edge of the underlying muscular coat is also necrotic and the latter is also somewhat thickened. Undermining has not yet appeared.

PLATE 24, FIG. 4. Photograph of a section of the undermined edge of the upper ulcer in Fig. 1. The wedge-shaped thickening of the submucous tissue is well seen, and also the undermining of the edge by the separation of necrotic tissue.

FIG. 5. Photograph of the stomach of Case 2. Towards the upper edge of the specimen is a small ulcer, the lower edge of which is undermined and raised and the upper edge sloping and partially cicatrized. The two oval ulcers to the right are almost healed. On the left-hand side in a corresponding situation the mucous membrane is superficially scarred.

FIG. 6. Photograph of a section of the undermined edge of the upper ulcer in Fig. 5. There is thickening of the submucous tissue and also of the peritoneum. The undermining is due to the separation of sloughs from the side of the ulcer and not to retraction of the muscular coat, which is projecting into the cavity of the ulcer.

FIG. 7. Photograph of the stomach of Case 3. The lower edge of the perforated ulcer is shallow and terraced, and the opposite edge a little thickened and undermined, and towards this side is situated the perforation. The three duodenal ulcers are easily distinguished. The photograph is rather too small to show the other lesions in the stomach.

PLATE 25, FIG. 8. Photograph of the ulcer of Case 4. The edges of the ulcer are quite smooth all round. The upper edge is undermined and clean; the lower edge sloping but not terraced. On section the ulcer is seen to be filling up all round with granulation tissue and the epithelium growing inwards over the base.

FIG. 9. Photograph of a section of the edge of the ulcer of Case 5. The whole base is composed of granulation tissue, and a single layer of epithelial cells can be seen growing over the base from the mucous membrane of the edge of the ulcer.

FIG. 10. Photograph of the ulcer of Case 8. Both cardiac and pyloric orifices are visible and the ulcer occupies a large part of the small curvature. Lobules of the pancreas are showing through in the base. The pyloric edge is undermined, and the cardiac shelving and becoming terraced by the separation of thin sloughs. This terracing can be seen better on section, as it is masked by the great thickening of the wall of the stomach. At the edge of the ulcer on the anterior wall large sloughs are separating and causing undermining of this edge.

PLATE 26, FIG. 11. Photograph of the undermined edge of the ulcer in Fig. 10. Enormous thickening of the submucous tissue is seen, and also of the peritoneum. The undermining has been produced by separation of sloughs from the sides of the ulcer.

FIG. 12. Photograph of a section of the right edge of the ulcer in Fig. 10. A large slough is in process of separation, which will lead to undermining of the edge.



FIG. 1



FIG. 2

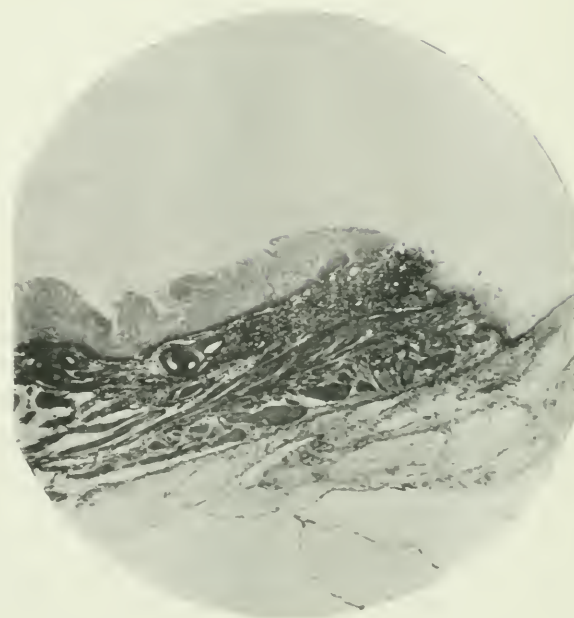


FIG. 3



FIG. 4



FIG. 6

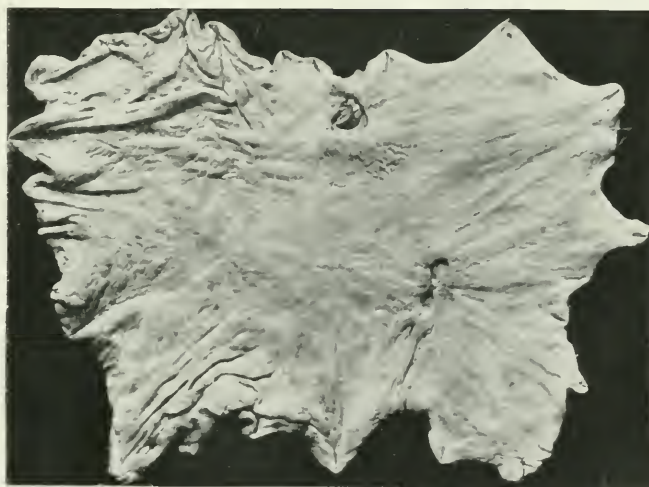


FIG. 5



FIG. 7

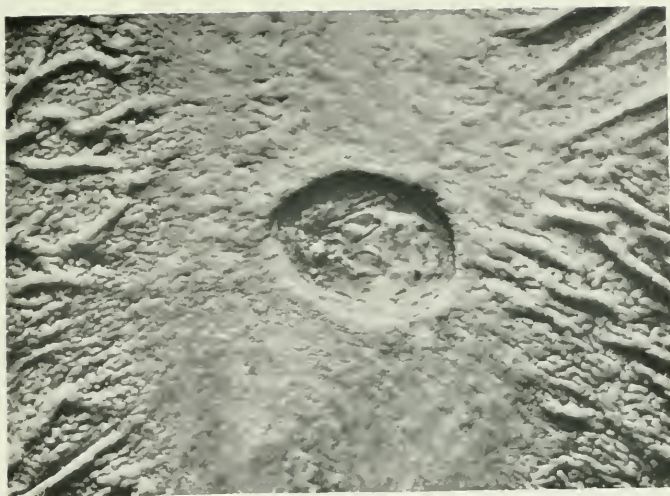


FIG. 8



FIG. 9

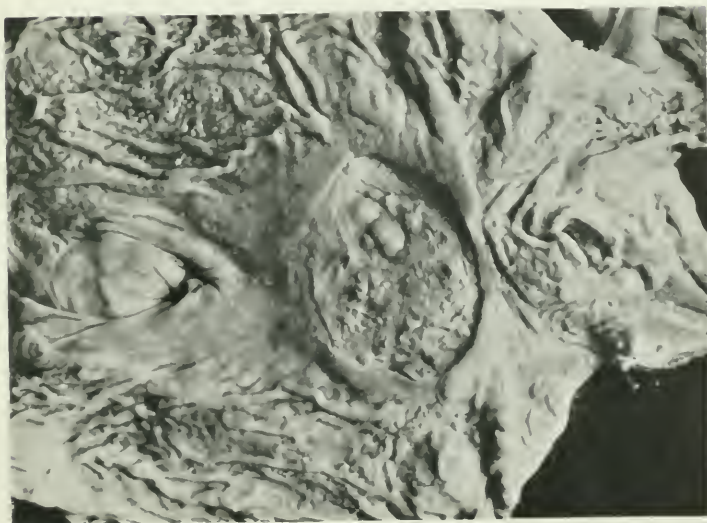


FIG. 10

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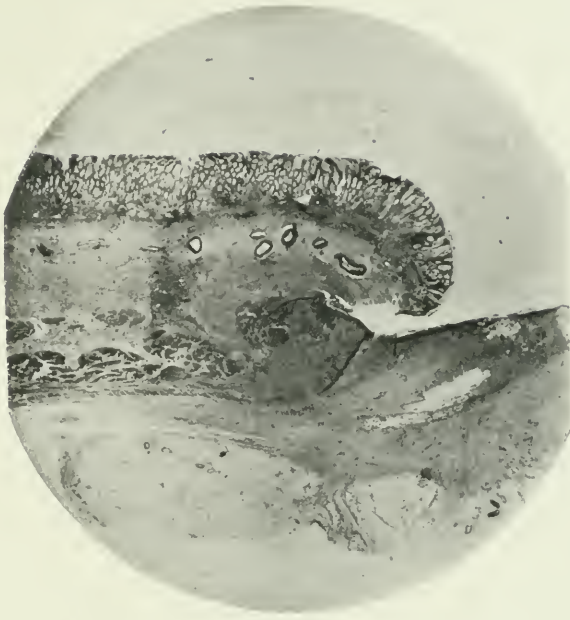


FIG. 11

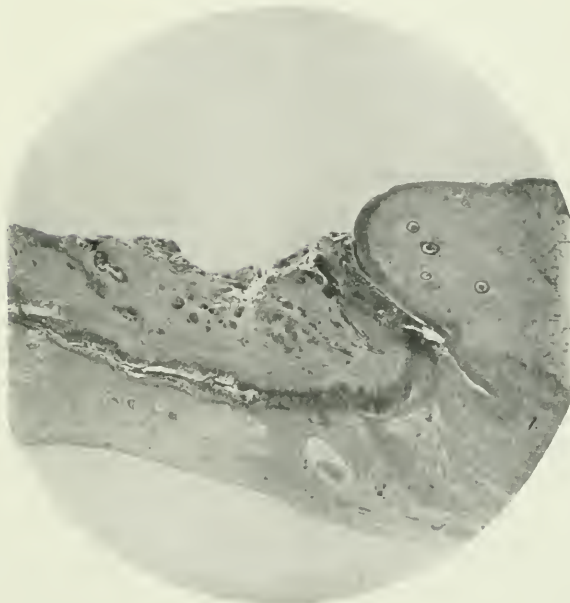


FIG. 12

No. 20

[*Reprinted from the Journal of Physiology,*
Vol. XLIV. No. 5, 1912.]

erding from the foramen. By March's
lowed a very considerable amount of
Seven days later the animal was killed, and the brain perfused
cent. alcohol.

THE CONTROL OF THE SUPRARENAL GLANDS BY
THE SPLANCHNIC NERVES¹. BY T. R. ELLIOTT,
M.D.

(From the Research Laboratories of University College,
Hospital Medical School.)

THERE is no clear knowledge² at present with regard to the share taken by the suprarenal glands in resisting various processes that are harmful to the body. For the last two years I have tried to gain some light on this question by analysing the state of exhaustion to which the human suprarenals are reduced in the different conditions leading to death in Hospital cases. Attention was paid chiefly to the loss of the normal load of cortical "lipoid" substance and of the adrenalin in the medulla, the gross total of the latter being measured quantitatively by physiological assay.

Unfortunately the conditions of fatal disease in man were found to be too complex to permit of simple analysis. Broadly summarising the results, it appeared that the glands suffered rapid exhaustion in cases of any microbic fever, of repeated simple hæmorrhage, and of surgical shock: but to distinguish clearly the value and nature of each of these factors was impossible. I therefore tried to reproduce each separately on experimental animals, in which the relationship of the nervous system to the glands could at the same time be studied.

Method. Cats were used in all the experiments. The lipoid in the cortex of the cat³ is never so abundant as in the human gland: changes in its distribution were observed histologically, but they did not seem to follow any special cause, and they will be referred to only incidentally in this paper. It was therefore to the adrenalin content of the medulla that attention was in the main directed.

¹ A preliminary account of the results has been given in *Proc. Physiol. Soc. This Journ.* XLIII. p. xxvii. 1912.

² Reference is made here only to papers which bear directly on points under discussion, for Biedl's admirable monograph (*Innere Secretion*, Wien, 1910) completely reviews all work up to date.

³ Elliott and Tuckett. *This Journal*, xxxiv. p. 351. 1906.

Roughly both lipoid and adrenalin content could be gauged by inspection of the cut surface of the gland after hardening it in a mixture of potassium bichromate solution and formalin (Orth's or Kohn's fluid). The fatty area is then visible as a white shell at the periphery, together with radiating streaks, as a rule, around the medulla: and the medulla takes a deep brown tint, varying patchily to a light yellow as exhaustion of its adrenalin progresses. The irregular distribution of the chromaffine reaction in the cells of a partially exhausted gland is very noticeable under the microscope, where exhaustion is generally found to occur earliest in the masses of cells adjacent to the largest veins.

But the histological method is inadequate. I consequently determined the actual amount of adrenalin that could be extracted from the glands after various phases of activity. The method used is capable of considerable accuracy. Briefly, it was as follows:

The suprarenals were excised, dissected clean, weighed, and each ground up with a little sand and Ringer's solution in a mortar. The extract was carefully washed out in a total volume of 15 c.c. This was boiled quickly, so as to avoid loss of fluid by evaporation, and filtered through glass wool. Sufficient extract, about 1.5%, was thus obtained for several injections. The extract was not acidified, and the estimation was always made as soon as it had cooled. Precisely similar vessels were used for each of a pair of glands; and the figures obtained, right and left glands in a normal cat giving exactly equal results, prove that the method of extraction was relatively satisfactory.

The absolute quantity of adrenalin in the gland was perhaps represented also with fair accuracy by the results, for the loss of adrenalin in the coagulated gland substance and sand may have been approximately compensated for by the concentration of the extract in boiling: this amounted usually to 1 or 1.5 c.c. on 15 c.c., and it was not made good by the addition of an equivalent volume of Ringer's solution. The error due to this concentration, if considered alone, would make the adrenalin content of a gland appear about .02 mgm. greater than it should be.

For the quantitative estimation of the adrenalin in the solution two methods are open, colorimetric being quite useless.

(1) The solution may be greatly diluted until the minimal strength is reached, which just affects some organ that reacts with great delicacy and certainty. The enucleated eyeball of the frog was suggested by Meltzer and used especially by Ehrmann. Its use has been often

criticised, and it is beyond doubt unsatisfactory. Best is the isolated uterus of the guineapig, as employed by Dale: but the chief value of this lies in its being an admirable test for the presence or absence of adrenalin. It is for qualitative rather than quantitative work.

(2) The actual concentration may be at once measured by intravenous injection into a cat. Under suitable conditions the resulting rise of blood-pressure varies directly with the amount of adrenalin injected. Some years ago I employed this method¹ with tolerable accuracy: the improvements suggested by Dale's experiments make it more reliable. After preliminary ether anæsthesia, the brain of a cat was destroyed by pushing a probe upward through the foramen magnum: a tracheal cannula was then inserted and artificial respiration commenced, both vagi being cut. The blood-pressure is now high, about 140 mm. of mercury. After a little delay, a long probe is then passed from the orbit, through the cranial cavity, and down the spinal canal to about the 4th thoracic segment. The blood-pressure soon falls to 40 or 50 mm.; and the circulatory system then will respond with the accuracy of a chemical balance to any dose of adrenalin. If only the medulla and brain are destroyed, the reflex machinery of the spinal cord often tends to prolong a blood-pressure rise induced by adrenalin and carry it on unduly in a series of rhythmic curves which hinder the estimation. On the other hand, if the cord be completely destroyed to the sacral end, the peripheral dilatation of the vessels is often so great that the heart ceases to beat, and in any case the blood-pressure rise caused by adrenalin becomes slow and irregular. A slight tone must, therefore, be present in the vessels for the reaction to be reliable. Any irregularity in the reactions is best dealt with by rejecting the animal and making a fresh preparation.

The injection was made into the external jugular vein by a cannula in connection with a burette of Ringer's solution.

It is necessary that the injections should be made as nearly as possible in equal times, and this was done by listening to a metronome beating seconds. The volume of solution containing adrenalin injected through the side needle was 1 c.c. in 5 seconds, which was at once

¹ This *Journal*, xxxii. p. 447. 1905. In a table of the maximum rises of blood-pressure attained by adrenalin under ether or urethane (*loc. cit.* p. 448), I was inclined to regard such height as the greatest which the muscles of a cat's circulation could attain. This was wrong. Adrenalin gives a rise to 300 mm. But the extreme stimulation of all the vaso-constrictor nerves and cardiac accelerators, caused by the passage of a narrow probe down the spinal cord, will raise the blood-pressure to 400 mm. in a cat free from anæsthetic after preliminary destruction of the brain.

washed through by 5 c.c. from the burette in the next five seconds. The injection fluid was simply at room temperature, and when introduced alone it did not affect the blood-pressure.

The curve of blood-pressure rise was inscribed on a kymograph, which was then turned back by hand, and the next injection made so that the curves should overlies one another. Identity of reaction requires that the curves should coincide in length as well as in height. As a standard solution any of the commercial preparations could be used. I preferred Höchst's synthetic suprarenin, .1 %, which for injection was diluted to .0025 %, so that 1 c.c. (.025 mgm.) gave a maximal rise of blood-pressure.

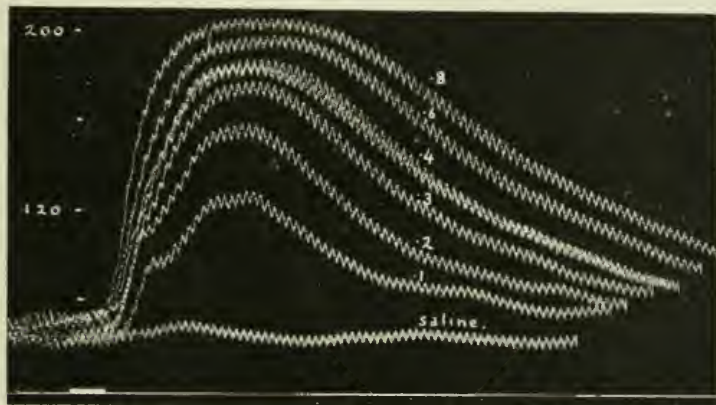


Fig. 1. Pithed cat. Gradation of response to increasing doses of a standard solution of suprarenin, .0025 p.c. The injections were made in succession from the lowest curve upwards; after 0.8 c.c. again 0.4 c.c. was injected, and the resultant curve is seen to coincide very closely with that previously obtained with 0.4 c.c.

The subjoined curves (Figs. 1 and 2) will illustrate the progressive increase in amplitude of the curves as the dose of suprarenin is increased, and they show that there is surprisingly little fatigue in the reaction. No time for recovery need be allowed, so soon as the blood-pressure has fallen to its original level. When the blood volume has been increased by the injection of 50 c.c. Ringer, it is well to abstract about 30 c.c. of blood and wait a short time for recovery. Generally 1 c.c. of the extract was injected, then such amount of the standard, .6 or .8 c.c., with saline up to 1 c.c., as was thought likely to give a similar reaction. With one curve above and one below that of the extract, it was usually sufficient to deduce the exactly equivalent amount of the standard by

interpolation and not to try exactly to duplicate the curve. The first amount of the extract was then injected again, to test whether the reaction was satisfactory and corresponded exactly with the first. This it should do.

Several estimations can easily be made on the same cat, so that not only was each of a pair of glands assayed on the same animal, but also glands from four or five cats, that had been subjected to different conditions of experiment on the same day, could be contrasted with one another under the same conditions of assay. This gave full value to the

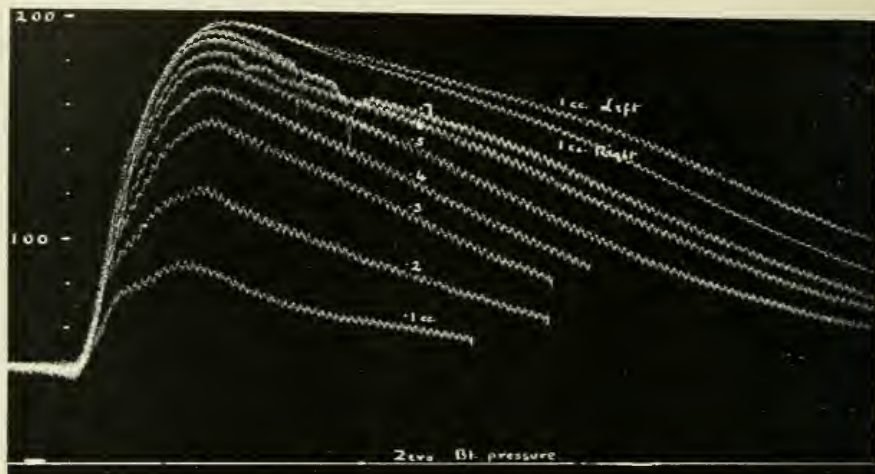


Fig. 2. A graded series of curves like the last, but with a slightly different type of reaction from the test cat. After 0.7 c.c. there were injected first 1 c.c. of the extract of the left suprarenal of another cat, and then 1 c.c. of an extract from the right gland. The two glands contained nearly equal amounts.

contrasting experiments, even if there were any doubt as to the absolute value of the adrenalin estimations; and it was an economy of working time. Under favourable conditions and by the exercise of some patience, the adrenalin content of a cat's gland could be assayed to an accuracy of .01 mgm., and always, at any rate, to .03 mgm. This form of adrenalin estimation naturally precluded any observations on the distribution of the cortical fat.

NORMAL GLANDS.

In an earlier paper¹ I have given a series of weights of suprarenals from a number of cats, and remarked on the slight difference in weight between right and left glands, together with the considerable increase in size with bodily growth, especially in the female. These differences were seen to be mainly due to cortical growth, although there was also some increase of the medulla. The total adrenalin content varies much more widely than the size of the medulla, for it fluctuates greatly from time to time in the same animal: very roughly it is about one-thousandth of the weight of each gland.

In nearly all intact animals the residual adrenalin is exactly equal in the right and left glands.

The highest yields were always found in cats that had been in the laboratory a week or more, resting quietly each in a single cage and being well fed. For example:

- (1) Good tempered cat, in stock one week: killed suddenly.
 Right gland .20 gm. = .32 mgm. suprarenin.
 Left gland .195 gm. = .32 ,, ,,

Recent admissions on the other hand were always sulky for a day or so, ready to snarl at their comrades, and very suspicious of their surroundings. In such, though their general bodily conditions might be good, the adrenalin value was always lower, *e.g.*

- (2) Right gland .21 gm. = .15 mgm. suprarenin.
 Left ,, .22 gm. = .14 ,, ,,

At various times 16 normals were examined, and only three of these gave a difference of as much as .02 mgm. between the two sides. The assay results for an adult cat were on an average, weight of each gland .2 gm., and adrenalin = .22 mgm.

EFFECT OF FRIGHT.

My first endeavour toward the analysis of pathological conditions was to examine the effect of fever alone without the complications introduced by microbic toxins. For this purpose I used the well-known pyretic drug β -tetrahydronaphthylamine hydrochloride. It failed to produce the desired effect. Two or three c.c. of a 2% solution injected subcutaneously did not raise the rectal temperature of a cat by more

¹ Elliott and Tuckett. *This Journal*, xxxiv. p. 336. 1906.

than a degree, while it caused the most obvious and persistent excitation of certain plain "sympathetic" muscles. The pupils are dilated to the utmost, and the eyeball is protruded: the whiskers are set stiffly erect, and the hairs down the back and on the tail are all raised. At times there is a tendency to lacrymal secretion, and the animal salivates a little. The body muscles show no tremor, nor unsteadiness: but the cat presents all the external features and attitude of persistent, wide-eyed alarm. Such, too, is its psychological state. Left alone, it may cry at intervals: snarls and hisses greet any one who approaches the cage. Next day the effect of the drug has passed away; the cat regains its equanimity and eats freely. β -tetra in the cat, then, causes fear and stimulation of the sympathetic muscles, but not fever.

During its action, the suprarenal glands suffer partial loss of residual adrenalin. On account of the varying load of adrenalin, upon which emphasis has already been laid in respect of different cats in different emotional states, it is of little value to quote figures for a normal cat under the influence of the drug, for the exhaustion is not complete.

It was found that the exhaustion was affected by central impulses passing through the splanchnic nerves, and this provided a clear method of demonstrating the action.

Splanchnic innervation. In a series of cats the splanchnic nerves were cut. This was done through a lumbar incision without opening the peritoneal cavity. The major splanchnic was identified and dissected down to the semilunar ganglion: the latter was then hooked up and all the preganglionic nerves to it divided. The dissection needs to be thorough, lest the minor collateral strands that cross the aorta from the lumbar sympathetic, or even the minor splanchnic itself, escape section. No blood vessels were divided, and care was always given to preserve the great lymphatic vessels behind and above the semilunar ganglion. The suprarenal itself was not interfered with at all. Probably the nerves were all divided in their preganglionic course¹.

It will be seen from the subsequent results (cf. chiefly Exps. 10 and 21) that the mere dissection in itself did not affect the functions of the suprarenal gland. None the less, as it might be urged that harm was

¹ Nerve ganglion cells are always present in the medulla. Dogiel figures these (*Arch. f. Anat. u. Physiol.* p. 90, Fig. 8, B. 1894) as being definitely on the course of the numerous medullated nerves that lie in the medulla of the gland. Perhaps all the nerves external to the gland are preganglionic, and the glandular fibres have no cell stations in the semilunar ganglion.

done by cutting tissues so close to the suprarenal, in many of my experiments, where the cat was not required to live after the operation, the sympathetic nerves were divided within the thorax just before they pierce the diaphragm. The recognition of the nerves in this situation is even easier than in the abdomen, and both right and left trunks can be divided, if necessary, from an opening on one side of the thorax, since the contralateral trunk is easily seen when the thoracic aorta is raised from its bed. Section of the splanchnics in the following experiments means division below the diaphragm, except where it is specially stated to have been done within the thorax.

The vagus has no direct anatomical connection with the suprarenals, and consequently experiments were not made directly to test its control. But in the course of my various experiments no difference was ever observed to depend upon the chance whether the vagi were cut or uncut.

After the operation the animals soon regained perfect health, and their suprarenals in consequence were always loaded with adrenalin to a high figure. Mere section of the nerves does not affect the adrenalin load in a quiet animal. Examples are:

- (3) Left splanchnics cut 1 day.
 Right gland .13 gm. = .32 mgm. suprarenin.
 Left ,, .13 gm. = .33 mgm.
- (4) Left splanchnics cut 2 days.
 Right gland .265 gm. = .37 mgm.
 Left ,, .27 gm. = .37 mgm.
- (5) Left splanchnics cut 11 days.
 Right gland .12 gm. = .17 mgm.
 Left ,, .11 gm. = .17 mgm.
- (6) Right splanchnics cut 14 days.
 Right gland .2 gm. = .30 mgm.
 Left ,, .2 gm. = .30 mgm.

The changes associated with *pregnancy* do appear to make some call upon the suprarenals, for the glands are larger in the multiparous female than in the male. Yet a healthy parturition, in itself, does not exhaust them.

- (7) Left splanchnics cut 11 days.
 Ten days after the operation she gave birth to two kittens, apparently without any trouble. Killed 20 hours after parturition, when she was contentedly suckling the kittens.
 Right gland .25 gm. = .30 mgm.
 Left ,, .25 gm. = .30 mgm.

However, many conditions can be induced in which a differential loss of adrenalin occurs, and one means to that end is the subcutaneous injection of β -tetra with its resultant fright.

- (8) Right splanchnics cut 15 days.
2 c.c. 2% β -tetra injected 8 hours, and 2.5 c.c. 4 hours before death. Moderately angry. Killed suddenly.
Right gland .23 gm. = .30 mgm.
Left ,, .21 gm. = .15 mgm.
 - (9) Left splanchnics cut 11 days.
3 c.c. β -tetra 24 hours before death. Very angry. Killed suddenly.
Right gland .22 gm. = .07 mgm.
Left ,, .22 gm. = .19 mgm.
 - (10) Left major splanchnic cut 18 days.
3 c.c. β -tetra 24 hours before death. Very angry. Killed in 15 minutes by 1.2 mgm. strychnine.
Right gland .250 gm. = .18 mgm.
Left ,, .235 gm. = .19 mgm.
- This illustrates what was seen in other cases, namely that section of the major splanchnic alone did not suffice to prevent exhaustion of the gland.
- (11) Right splanchnics cut 13 days.
5 c.c. β -tetra 7 hours before death. Killed. Glands examined histologically. Fat was equally distributed in the usual zones in each, but the left gland contained absolutely no chromaffine substance, whereas the right took a deep brown stain.

This loss of residual adrenalin was, therefore, to be regarded as the result of central nervous impulses, and not caused by direct peripheral stimulation of the gland cells. It was not due to fever, but might have been associated either with the emotion of alarm, or with the excitation of the hair and other sympathetic muscles. Jonnescu¹ emphasised the fact that the general stimulating action of the drug is on muscles with sympathetic innervation and not on gland cells; and he suggested, from degenerative section experiments, that the seat of its action is partly central, and partly peripheral. The latter is more or less true. After excision of the superior cervical ganglion, the effects on the denervated pupil are certainly almost as full as on the normal eye; but this may be a response to the adrenalin liberated from the suprarenals. No excitation results from direct application of the drug to the cells of the superior cervical ganglion. Still the general sympathetic excitation is slight: injected intravenously it produces, in small doses, only a slight rise of blood-pressure, and a rapid fall with bigger amounts: nor is there any manifest rise when it is injected subcutaneously. Hence it does not seem very probable—though the

¹ *Arch. f. exp. Path. u. Pharm.* LX. p. 345. 1909.

hypothesis cannot be excluded—that the adrenalin exhaustion ought to be regarded as a discharge directly required in consequence of the prolonged excitation of an area of muscle with sympathetic innervation.

There remains the emotional alarm, a feature very prominent in the cat, much less obvious in the rabbit and guineapig¹, where it was, however, noticed by Pembrey and Mutch². This might be either an emotion of central origin, or, on James' theory, the mental expression of the impulses generated by the drug's continuous peripheral excitation of the muscles of emotional expression. An experiment somewhat similar to Sherrington's³, was made to test this. The spinal cord of a cat, which had been previously proved to give a full emotional reaction to β -tetra, was transected at the first thoracic segment. Ten days later 2.5 c.c. of 2% β -tetra were injected subcutaneously. The usual peripheral reaction was seen, and the animal, which had previously been peaceful, became very angry and bit its attendant.

Apparently, therefore, the emotion is centrally excited; and it seemed possible that it was this fright alone which led directly to the exhaustion of the suprarenal as an immediate means towards the expression of this emotion.

At Prof. Cushny's suggestion I made use of another drug which terrifies cats, *morphia*. Twenty mgm. of this impels a cat into ceaseless, wild, disordered movements that strongly suggest their origin in pressing hallucinations of dread. The animal gives no cry; it does not attack those who approach it; and, while its pupils are dilated, it evinces no other phenomena of peripheral sympathetic excitation. Yet the exhaustion of adrenalin via the splanchnic nerves is even more marked than with β -tetra, where, on the other hand, the peripheral stimulation is greater.

(12) Left splanchnics cut 9 days.

Morphia 20 mgm.: cat killed 8 hours later.

Right gland .205 gm.=.02 mgm.

Left ,, .200 gm.=.15 mgm.

¹ The pigeon does not respond by any indication of alarm, nor are its feathers displaced. In my own forearm, where adrenalin is quite effective, β -tetra produces no pilomotor effect and no vaso-constriction. I never used a large enough injection in myself to cause any sensation of alarm, being to some extent deterred from doing so by the curious fact that subcutaneous injection of β -tetra invariably causes acute gastric ulcers in the guineapig.

² This *Journal*, XLIII. p. 123. 1911.

³ *Integrative action of the Nervous System*, p. 260. London, 1909.

- (13) Left splanchnics cut 17 days.
 Morphia 20 mgm.: killed 6 hours later. (Cf. Fig. 3.)
 Right gland ·195 gm. = ·07 mgm.
 Left ,, ·190 gm. = ·22 mgm.
- (14) Left splanchnics cut 40 days.
 Morphia 30 mgm.: killed 8 hours later.
 Right gland ·205 gm. = ·02 mgm.
 Left ,, ·210 gm. = ·12 mgm.

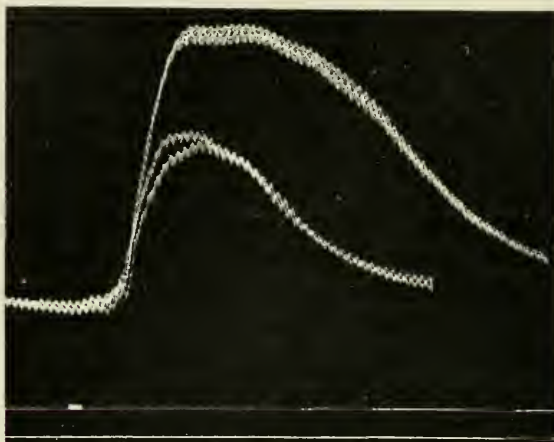


Fig. 3. From Exp. (13). Left splanchnics cut, and right gland exhausted by fright of morphia. Labelling the curves A, B, C, D from the topmost downwards, they correspond respectively to

- (A) 1 c.c. of left gland,
 (B) 0·6 c.c. of ·0025 % suprarenin,
 (C) 1 c.c. of right gland,
 (D) 0·2 c.c. of ·0025 %,

and they were injected in the order C, A, D, B.

As a control to this, strychnine was injected in successive small doses of ·4 mgm.: the result was a little muscular rigidity, but no alarm. A final dose of ·6 mgm. suddenly killed the cat in ten minutes.

- (15) Left splanchnics cut 17 days.
 Strychnine 1·8 mgm. in 6 hours. Died.
 Right gland ·2 gm. = ·26 mgm.
 Left ,, ·2 gm. = ·26 mgm.

There can, then, be no doubt of the fact that a differential exhaustion of the glands, when the splanchnics have been divided on one side, is caused by morphia and by β -tetra, drugs which have the common action of exciting the cat to emotional alarm. Experiments will be described in subsequent pages, which tend to justify the view

taken, that this exhaustion is directly due to the fright caused. The most direct method of analysis would be that of inducing emotional fear at once, as by vexing the cat with a dog. This I have not done. But evidence of that nature is supplied by the experiments of Cannon and de la Paz¹ in which, by a very delicate and ingenious method, they showed that the emotion of anger or fear is associated with the appearance of adrenalin in the blood from a cat's suprarenal vein.

Rise of blood-pressure. The results with β -tetra could be explained on either of two views:

(a) That a large area of sympathetic muscle is thrown into action, in part directly by the drug and in part indirectly by the nervous system, and that the suprarenal gland secondarily receives a call through the splanchnic nerves to contribute its help to that peripheral action.

(b) That the whole machinery of sympathetic musculature and of the suprarenal glands may be at once and simultaneously excited by a universally distributed impulse, as in emotional alarm, the call on the suprarenal being then made directly and urged whether the peripheral musculature responds or not.

Emotional alarm could be present with either (a) or (b), though the latter has in the preceding pages been taken as the provisional explanation. The hypotheses at once suggest further experiments, in which the excitation of the sympathetic musculature shall be caused independently of alarm. The simplest is that of producing a general and prolonged rise of blood-pressure. Stimulation of the central end of a large nerve, such as the cut sciatic, does not cause a big rise. I therefore endeavoured to reproduce the conditions of cerebral hæmorrhage in man, in which a prolonged rise in blood-pressure is often caused by the injurious presence of the outpoured blood.

A cat was pithed by pushing a sharp stilette through the foramen magnum and forwards to the frontal lobes, where a lateral movement transects the crura cerebri. If the animal's head be fully flexed during this operation, the instrument will pass through the cerebellar peduncles above the medulla, so that independent respiration is preserved. The blood-pressure, after a transient enormous rise (associated with sweating from the pads), falls to a high level of 140 or 150 mm.: both vagi are then divided, and the splanchnic nerves cut on one side. The cat is covered up on a warm box, ultimately killed, and the adrenalin content of the two suprarenals assayed. Exhaustion

¹ *Amer. Journ. Physiol.* xxviii. p. 64. 1911.

occurs quickly on the side which is still in connection with the spinal cord.

- (16) Pithed 6 hours. Natural respiration throughout. Vagi and left splanchnics cut. Blood-pressure slowly fell from 170 to 110 mm. No rise of temperature. Glycosuria.
 Right gland .12 gm. = .03 mgm.
 Left „ .125 gm. = .19 mgm.
- (17) Pithed 4 hours. Left splanchnics cut. Natural respiration throughout. Blood-pressure 140 to 150 mm.
 Right .22 gm. = .11 mgm.
 Left .20 gm. = .23 mgm.
- (18) Left splanchnic nerves cut 40 days.
 Pithed 4 hours: artificial respiration needed. Vagi cut. Blood-pressure for 1 hour at 110, for 3 hours at 80 to 60 mm.
 Right .24 gm. = .15 mgm.
 Left .23 gm. = .30 mgm.

The same effect was also observed when the cerebral hemispheres alone were destroyed by pushing the stilette through the temporal fossa immediately across the crura cerebri, and without direct damage of the brain structures below the tentorium.

- (19) Transtemporal pith. Artificial respiration. Vagi and left splanchnics cut. Blood-pressure 140 for $3\frac{1}{2}$ hours. Slight glycosuria: no fever.
 Right .25 gm. = .19 mgm.
 Left .27 gm. = .32 mgm.
- (20) Pithed 6 hours. Natural respiration. Left splanchnics cut. Blood-pressure 160 to 140 mm. Glands hardened in Orth's fluid.
 Right colourless.
 Left full chromaffine tint. Fat equal in each.

To prove that the dissection around the semilunar ganglion did not hinder loss of adrenalin from the gland of that side by interference with its circulation, the following experiment was made.

- (21) Pithed 4 hours. Natural respiration: vagi cut. Blood-pressure 160 to 140. Right splanchnics cut. Left splanchnics fully dissected out, but not cut.
 Right .26 gm. = .34 mgm.
 Left .25 gm. = .04 mgm.

Lastly, the sympathetic nerves were cut within the thorax, so as to avoid all chance of interference with the tissues around the suprarenal gland.

- (22) Pithed 5 hours. Left splanchnics cut within thorax. Natural respiration re-established.
 Right .165 gm. = .11 mgm.
 Left .14 gm. = .26 mgm.

From these, and other experiments with invariably the same results, it was certain that the damage to the brain led to exhaustion of the suprarenal that was still in nervous connection with the spinal cord. But there still remained unsettled the distinction between the possible explanations (a) and (b); for the exhaustion was accompanied by a persistent rise of blood-pressure and steady constriction of the muscles of the blood vessels.

With the hope of removing this vasoconstriction I injected into the veins β -iminazolyethylamine, the histamine which Dale and Laidlaw¹ have shown to be so powerful a depressor of the cat's systemic blood-pressure, while it either leaves untouched or stimulates the known sympathetic glandular nerves. The cat was pithed, β -i injected so as to reduce the blood-pressure to a low value, and then the left splanchnics cut. Exhaustion of the contralateral suprarenal still resulted.

- (23) Pithed: natural respiration: blood-pressure 170 mm. β -i, 0.6 mgm. injected: blood-pressure fell to 60. Left splanchnics cut. Killed 2 hours later, blood-pressure being about 40 mm. all the last hour. No glycosuria.

Right .18 gm. = .03 mgm.

Left .14 gm. = .16 mgm.

- (24) Pithed 4 hours. β -i, in all 2.3 mgm. of the base. Blood-pressure fell from 150 to 50. Left splanchnics cut. The vaso-constrictors were not paralysed, for crushing the leg bones caused an immediate reflex rise of pressure from 50 to 160.

Right .15 gm. = .01 mgm.

Left .15 gm. = .11 mgm.

Intravenous injection of β -i, therefore, does not serve to make the desired distinction. During its action the blood-pressure is very low, but the vaso-constrictors are not fully paralysed, and the nervous exhaustion of the suprarenal proceeds as usual. As will be shown later, the drug does not directly excite the gland cells to excretion.

This view, that cerebral irritation may directly excite the suprarenals, is not a new one. André Mayer² elaborated Blum's³ suggestion that the glycosuria of Bernard's "diabetic puncture" might be caused by the splanchnics playing on the suprarenals, and liberating adrenalin which in its turn would act upon the liver to produce sugar. Nishi⁴ was guided by a similar opinion, when he showed that the subcutaneous injection of diuretin failed to cause glycosuria in a rabbit after excision of its suprarenals. Cannon⁵ and his collaborators further proved that emotional fear led to glycosuria in cats, but

¹ This *Journal*, xli. p. 318. 1910-1911.

² *C. R. Soc. de Biol.* p. 1123. 1906; and p. 219. 1908.

³ *Pflüger's Arch.* xc. p. 617. 1902.

⁴ *Arch. f. exp. Path. u. Pharm.* lxi. p. 401. 1909.

⁵ *Amer. Journ. Physiol.* xxix. p. 280, and p. 274. 1911.

failed to do so when the suprarenals had been previously excised. The sole contrary evidence is that of Wertheimer and Battez¹, who state that they were able to cause glycosuria in cats by the Bernard puncture after removal of the suprarenals. The bulk of evidence is in favour of the view that brain injury or excitation discharges the suprarenals, and so may produce moderate glycosuria.

Sugar always appeared in the urine of my pithed cats, though its amount was much reduced in the cases where β -i had been injected with a consequent fall of blood-pressure and diminution of urinary secretion.

EFFECT OF ANÆSTHETICS AND OF OTHER DRUGS.

From the experiments already cited, it appeared probable that the alarm in a cat attendant upon the induction of anæsthesia by ether or chloroform would lead to some exhaustion of residual adrenalin. But there was no reason to suppose that the exhaustion would proceed subsequently while the brain was in a state of deeper anæsthesia. Such, however, was found to be the case.

Ether.

- (25) Ether 6 hours: left splanchnics cut. Blood-pressure 160 to 140.
 Right gland .23 gm. = .11 mgm.
 Left ,, .23 gm. = .22 mgm.
- (26) Female, 2700 gms., which had kittened a day or two previously. Ether 3 hours.
 Left splanchnics cut: blood-pressure 140, but 50 in last hour.
 Right .45 gm. = .20 mgm.
 Left .45 gm. = .45 mgm.
- (27) Left splanchnics cut 9 days.
 Light ether 5 hours. No blood-pressure taken, so as to avoid all operative
 interference with the animal's tissues.
 Right .28 gm. = .13 mgm.
 Left .25 gm. = .21 mgm.

Other experiments were made with a slight variation from the usual type. A gland extract made in the ordinary way, and not acidified, was found to lose strength slowly on standing at room temperature—in four experiments the solution lost in six hours on an average .04 mgm. or roughly 20%. An excised gland kept on ice for six hours lost practically no adrenalin; whereas one kept at room temperature (17°) in a moist chamber lost about 30%. For example, the glands were both excised from a newly killed cat: that of the right side was at once assayed, .15 gm. = .22 mgm.: the left was kept at 17° C. for five hours and then extracted, .16 gm. = .15 mgm.

Since the glands on each side normally contain exactly similar amounts of adrenalin, and since an excised gland kept on ice suffers

¹ *Arch. internat. de Physiol.* p. 363. 1910.

very slight loss of adrenalin in a few hours, the following experiments were justified as illustrating the nervous control of adrenalin loss under ether.

(28) Ether. Right gland at once excised: left gland intact. Ether continued for 6 hours. Blood-pressure 110 to 90.

Right $\cdot 2$ gm. = $\cdot 26$ mgm.

Left $\cdot 2$ gm. = $\cdot 07$ mgm. (Cf. Fig. 4.)

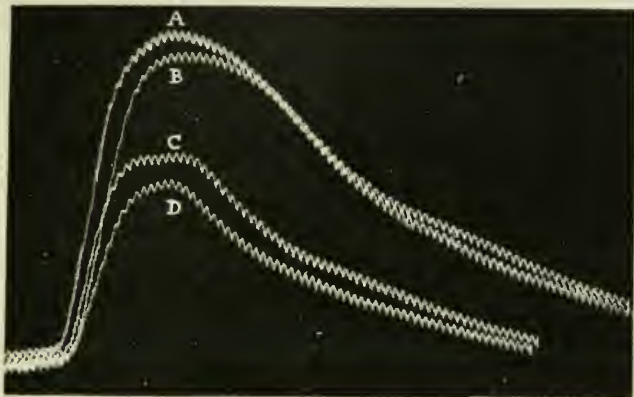


Fig. 4. From Exp. (28). Right gland excised, and left splanchnics cut. Ether anaesthesia for 6 hours, which exhausted left gland. Curves A, B, C, D from above downwards are respectively

(A) 1 c.c. of extract of right gland,

(B) 0.6 c.c. of $\cdot 0025\%$ suprarenin,

(C) 0.2 c.c. of $\cdot 0025\%$,

(D) 1 c.c. of left gland.

Injected in the order B, D, C, A.

The exhaustion of the gland left in the cat could be largely prevented by section of the splanchnic nerves.

(29) Ether. Left gland excised. Right splanchnics cut. Ether continued for 5 hours. Blood-pressure 110 to 130. Animal then killed.

Right $\cdot 16$ gm. = $\cdot 12$ mgm.

Left $\cdot 14$ gm. = $\cdot 11$ mgm.

(30) Ether. Left splanchnics cut, and right gland excised. Ether continued for 7 hours. Blood-pressure 140 to 130.

Right $\cdot 26$ gm. = $\cdot 23$ mgm.

Left $\cdot 30$ gm. = $\cdot 23$ mgm. (Cf. Fig. 5.)

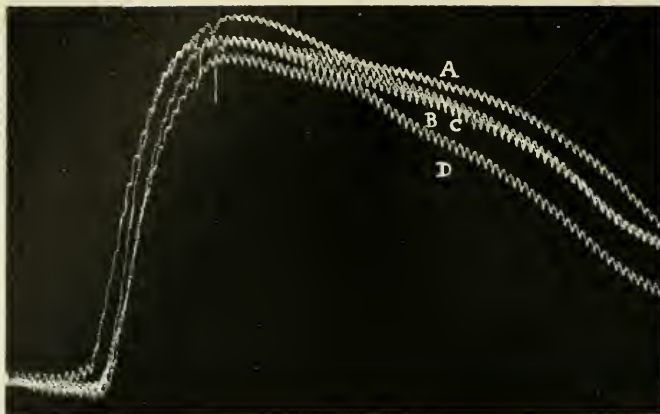


Fig. 5. From Exp. (30). Right gland excised, and left splanchnics cut. Ether anæsthesia continued for 7 hours, but no exhaustion of left gland. Curves are

(A) 0·7 c.c. of ·0025 % suprarenin,

(B) & (C) Closely overlapping, each 1 c.c. of left and right gland successively,

(D) 0·5 c.c. of ·0025 %.

Injected in the order B, C, D, A.

The exactness of this numerical coincidence was not a mere chance, for it was observed on every occasion.

- (31) Ether. Left splanchnics cut within thorax. Right suprarenal excised and placed in ice chest. Ether continued for 5 hours. Blood-pressure finally 140 mm.

Right ·23 gm. = ·27 mgm.

Left ·22 gm. = ·27 mgm.

Similar results were obtained with other anæsthetics.

Chloroform. Anæsthesia is induced much more quickly than with ether, and there is less struggling and holding of breath up to a stage of partial asphyxia. But the exhaustion of the suprarenal is fully as great as with ether, and is effected in the same way through the splanchnic nerves.

- (32) Chloroform 5½ hours: left splanchnics cut.

Right ·185 gm. = ·08 mgm.

Left ·175 gm. = ·21 mgm.

- (33) Chloroform 5 hours: left splanchnics cut within thorax, which was then closed and natural respiration re-established.

Right ·19 gm. = ·15 mgm.

Left ·18 gm. = ·26 mgm.

- (34) Left splanchnics cut 12 days by previous operation. Chloroform 2¾ hours. No blood-pressure taken.

Right ·22 gm. = ·17 mgm.

Left ·20 gm. = ·24 mgm.

- (35) Chloroform. Left splanchnics cut within thorax. Right suprarenal excised. Chloroform continued 5 hours, and cat killed when blood-pressure was 130 mm.

Right .23 gm. = .21 mgm.

Left .23 gm. = .21 mgm.

Urethane. Subcutaneous injection of this narcotic can be effected without much alarm of the cat, which passes slowly and drowsily into a state of unconsciousness. So the excitement of the first stages of anæsthesia by the volatile anæsthetics is avoided. Still the exhaustion through the nerves appears.

- (36) Urethane, 18 c.c. of 25 % subcutaneously. Left splanchnics cut 1½ hours later, when fully narcotised. Killed 4½ hours after this. Was perfectly quiet.

Right .12 gm. = .07 mgm.

Left .11 gm. = .13 mgm.

- (37) Urethane. Left splanchnics cut 2 hours later. Killed 6 hours after this, when blood-pressure was 106.

Right .185 gm. = .11 mgm.

Left .189 gm. = .28 mgm.

Pilocarpine. It would be of great interest to prove that some drug has power directly to stimulate the suprarenal medullary cells to excretion of adrenalin, for then the apparent general action of the drug on other tissues of the body would be complicated by the reaction secondary to the adrenalin liberated¹.

I have made several experiments upon this point, but failed to find proof that pilocarpine influences the adrenalin load in any way. Tschoboksaroff² also could find no evidence that pilocarpine excites secretion from the suprarenals.

- (38) Ether 4 hours: left splanchnics cut. Pilocarpine in successive doses of 5 mgm. up to 20 mgm. Very free secretion of saliva, tears, and sweat.

Right .26 gm. = .17 mgm.

Left .26 gm. = .26 mgm.

Here the only exhaustion was the ordinary effect produced under ether through the splanchnic nerves: the left gland with cut nerves retained a big load of adrenalin. Absence of evident exhaustion does not exclude some brief stimulus to excretion: for it will be shown later in this paper that faradisation of the splanchnic nerves does discharge adrenalin into the blood, but yet fails to produce very obvious exhaustion of the residual adrenalin.

¹ Cf. Dale and Laidlaw. *Proc. Physiol. Soc.* This *Journal*, XLIV. p. xii. 1912.

² *Pflüger's Arch.* CXXXVII. p. 59. 1910-1911.

- (39) Ether $2\frac{1}{2}$ hours: right splanchnics cut: left dissected out, but not cut. Pilocarpine in all 30 mgm. Profuse secretion of saliva, and twitching of body muscles.

Right $\cdot 195$ gm. = $\cdot 30$ mgm.

Left $\cdot 19$ gm. = $\cdot 24$ mgm.

In neither of these assays was allowance made for the small amount of pilocarpine that might be present in the suprarenal glands, for this would probably be the same in each, and could not affect the contrast result.

Physostigmine. This drug, according to the experiments of Tschoboksaroff on dogs, does increase the output of adrenalin even after section of the splanchnics. I could not find any trace of consequent exhaustion in cats.

- (40) Ether for 3 hours. Left splanchnics cut within thorax. Physostigmine in successive doses up to total of 14 mgm. Fair secretion of saliva: bodily twitchings: blood-pressure slowly sank to very low level.

Right $\cdot 17$ gm. = $\cdot 09$ mgm.

Left $\cdot 18$ gm. = $\cdot 15$ mgm.

- (41) Ether. Left splanchnics cut within thorax. Physostigmine 9 mgm. Died in $1\frac{1}{2}$ hours, with very low blood-pressure.

Right $\cdot 19$ gm. = $\cdot 08$ mgm.

Left $\cdot 20$ gm. = $\cdot 23$ mgm.

Histamine. This poison, β -iminazolyethylamine, has been discussed earlier in the paper. It has no direct exhausting action on the medullary cells.

- (42) Ether. Right suprarenal excised and placed on ice: left splanchnics cut within thorax. β -i in successive doses of $\cdot 5$ mgm. of the base, up to total of 4 mgm. in 3 hours.

Right $\cdot 2$ gm. = $\cdot 17$ mgm.

Left $\cdot 2$ gm. = $\cdot 15$ mgm.

Pituitary gland extract. There are some hazy views current as to the interaction of the ductless glands, and therefore it is desirable to know whether pituitary extract can stimulate excretion of adrenalin from the medullary cells, the more so inasmuch as its direct action on some gland cells has been illustrated by Ott's¹ discovery that it stimulates the mammary gland to rapid secretion.

- (43) Ether $4\frac{1}{2}$ hours. Left splanchnics cut within thorax. Pituitary extract, Burroughs' and Wellcome's 20 % preparation, given in successive doses up to total of 3 c.c.

Right $\cdot 35$ gm. = $\cdot 22$ mgm.

Left $\cdot 32$ gm. = $\cdot 32$ mgm.

This is practically the same differential result that would have been seen with the administration of ether alone for $4\frac{1}{2}$ hours. A second experiment gave a similar result.

¹ Cf. full analysis by Schäfer and Mackenzie. *Proc. Royal Soc. B*, p. 16. 1911: and *Quart. Journ. Exp. Physiol.* iv. p. 305. 1911.

Adrenalin. The intravenous injection of this substance in large quantities does not appear to influence either storage or loss of adrenalin from the suprarenals. There is certainly no direct action on the gland.

- (44) Ether. Right splanchnic cut within thorax and left suprarenal excised. Adrenalin then injected into jugular vein in successive doses of $\cdot 2$ mgm. until total of $3\cdot 5$ mgm. was reached in 4 hours. Blood-pressure rose generally to 220 mm.

Right $\cdot 205$ gm. = $\cdot 23$ mgm.

Left $\cdot 20$ gm. = $\cdot 23$ mgm.

The loss when the splanchnic nerves are uncut, is much the same as would be seen if the cat were left under similar conditions of ether anaesthesia and without the injection of adrenalin. The adrenalin has no apparent effect in saving the gland from exhaustion.

- (45) Ether. Left splanchnics cut within thorax. Adrenalin injected to total of $3\cdot 5$ mgm. in 3 hours. Blood-pressure rose at first to 350 mm., and later to 240. In this, as in the preceding case, numerous small hæmorrhages were caused in the cortex of the glands.

Right $\cdot 16$ gm. = $\cdot 03$ mgm.

Left $\cdot 15$ gm. = $\cdot 15$ mgm.

A statement of mine in an earlier paper¹, that the injection of adrenalin discharges the medullary cells, was a mistake due to ignorance of the loss under simple ether anaesthesia and experimental interference with the animal's tissues, conditions in themselves sufficient to produce the changes which I had attributed to the adrenalin.

Diphtheria toxin. Many observers have remarked on the hæmorrhagic congestion produced in the suprarenal glands of rabbits and guineapigs by the fatal action of microbic poisons, this being especially noticeable in death caused by diphtheria toxin. The view has in consequence often been urged that one function of the suprarenal may be to neutralise such toxins. For this the sole evidence is an old experiment of Walter Myers², that cobra venom is rendered harmless when triturated with suprarenal gland cells. This particular result, however, might be ascribed to the active oxidase in the suprarenal. There is no reason at all for believing that microbic toxins can be neutralised by an action of suprarenal cells, whether of the cortex or medulla. Noon³ showed this with regard to diphtheria toxin, and the fact has been confirmed by Ritchie and Bruce⁴, who added the

¹ This *Journal*, xxxii. p. 427. 1905.

² *Brit. Med. Journal*, p. 946. 1898.

³ This *Journal*, xxxiv. p. 332. 1906.

⁴ *Journal Exp. Physiol.* iv. p. 127. 1911.

supplementary observation that diphtheria toxin in its turn does not exert any destructive action on adrenalin.

None the less the relationship of the toxins to the suprarenals might conceivably be a close one, namely this, that they are not destroyed by the gland, but that they destroy the animal largely through its glands, throwing them out of action and so inducing circulatory depression and death.

Such a view would be supported by the observation of many workers, especially of the French school, that the suprarenals of guineapigs killed by various infections are emptied of adrenalin and often congested, as particularly with diphtheria toxin. And it would embrace my cases of various septic fevers in man, where the adrenalin load is quickly lessened and the cortical lipoid vanishes at once. But the view would postulate a complete exhaustion of the adrenalin that death might ensue: and the exhaustion is not complete. Ritchie and Bruce, indeed, do describe a complete exhaustion by diphtheria toxin in the guineapig. But it certainly does not occur in the cat, nor in man.

- (46) Diphtheria toxin, .15 c.c., injected subcutaneously. Cat died in 40 hours. Glands, which were a little congested, assayed 12 hours after death.
 Right .21 gm. = .14 mgm.
 Left .21 gm. = .15 mgm.

This animal had been in stock some time, and its glands should have contained probably .25 mgm. Some loss had, therefore, occurred over and beyond that due to post mortem changes in the 12 hours preceding their analysis. But the loss was much too slight to justify a belief that the animal succumbed to lack of adrenalin from its suprarenals. That the output of adrenalin from the glands can be maintained up to the time of death, and that the congestion does not simply lock it up inaccessibly within the gland, is proved by the subjoined experiments.

- (47) Left splanchnics cut 32 days. Diphtheria toxin .59 c.c. subcutaneously. Death in 17 hours. Glands equally and markedly congested: assayed at once.
 Right .27 gm. = .04 mgm.
 Left .23 gm. = .19 mgm.
- (48) Left splanchnics cut 34 days. Diphtheria toxin, .18 c.c., subcutaneously. Death in 30 hours. Glands assayed 3 hours later. Both slightly and equally congested.
 Right .26 gm. = .04 mgm.
 Left .27 gm. = .22 mgm.
- (49) Left splanchnics cut 24 days. Diphtheria toxin, .24 c.c., subcutaneously. Death in 38 hours. Glands assayed at once. (Cf. Fig. 6.)
 Right .35 gm. = .02 mgm.
 Left .32 gm. = .20 mgm.

- (50) Left splanchnics cut 24 days. Diphtheria toxin, .12 c.c. Death in 50 to 54 hours. Glands assayed about 4 hours after death.
 Right .23 gm. = .03 mgm.
 Left .215 gm. = .15 mgm.
- (51) Left splanchnics cut 24 days. Diphtheria toxin, .09 c.c., died in 70 hours. Glands congested, so as to resemble bluish red plums: assayed at once.
 Right .20 gm. = .06 mgm.
 Left .19 gm. = .15 mgm.

In these last five cats, which had been operated on, and were living quietly and happily in the laboratory, the adrenalin load of the glands should have been high. A slight loss occurred on the decentralised side, and much greater exhaustion on the side with nerves still intact. Soon after the injection, the animal refused food and moped. A similar period of moping would produce somewhat similar exhaustion in an

Fig. 6. From Exp. (49). Left splanchnics cut. Death by diphtheria toxin. Right gland alone exhausted. Curves are

- (A) 0.6 c.c. of .0025 %
 suprarenin,
 (B) 1 c.c. of left extract,
 (C) 0.1 c.c. of .0025 %,
 (D) 1 c.c. of right ex-
 tract.



otherwise healthy cat, doing so by impulses playing on the glands through the splanchnic nerves. The exhaustion caused by diphtheria poisoning seems to be of this nature. It is mainly produced through the splanchnic nerves, and only to a slight degree by a direct action of the poison on the glands: and probably it is an expression of the efforts made by the animal to combat the fall of blood-pressure and other changes due to the action of the poison elsewhere. In brief, the adrenalin exhaustion is secondary, an expression of the cat's struggle for life: it is not a primary factor leading to death. In respect of the cortex there is no conspicuous difference between the decentralised and the other gland. Each shows spreading of the lipoid, though no longer doubly refractive, more widely through the cortex, and cloudy degeneration of the cells.

DIRECT STIMULATION OF THE SPLANCHNIC NERVES.

The method of determining the residual content of adrenalin, after section of the nerves on one side, proves beyond doubt that the splanchnic nerves influence the amount of adrenalin in the suprarenal glands.

Accepting Dogiel's account of the anatomical connection of the splanchnic nerves with the medullary cells, and also the observation made first by Cybulski, 1896, and since confirmed by many others, that adrenalin appears in the blood of the suprarenal veins, several workers have sought to give a clear proof of the obvious deduction, namely that the splanchnics should control the excretion of adrenalin from the glands. All have attempted this directly, by electrical stimulation of the splanchnic nerves and analysis of the outgoing venous blood.

Biedl's¹ earliest experiments suggested that the splanchnics carried vaso-dilator fibres to the glands, but could not demonstrate any increased excretion of adrenalin. Dreyer², however, obtained positive results with dogs. So, too, did Tschoboksaroff³ in a very clear series of experiments, though he observed that after stimulation the gland on the stimulated side yielded a more potent extract, that is contained more adrenalin, than that of the other side. Waterman and Smit's⁴ observations on rabbits are too uncertain to require discussion. So the direct proof of the nervous action, by faradisation of the splanchnic nerves, rests upon the results reported by Dreyer and Tschoboksaroff with dogs, and those recently by Asher⁵ with rabbits.

Oddly, I have never succeeded in demonstrating more than a very slight loss in cats, when using the method of measuring the residual adrenalin. The effect of faradising the nerve directly is certainly much less than that caused indirectly through the machinery of central nervous control. Consequently, when a cat is kept under ether and the cut splanchnics faradised on one side, the contralateral gland ultimately is found to be the more exhausted. This result met me when first I tried stimulation of the splanchnic nerves, and it seemed inexplicable until later the reflex exhaustion under ether itself was analysed and found to be the cause of the paradoxical effect. Tschoboksaroff also observed it, though he explained the contrast by ipsilateral anabolism rather than contralateral katabolism.

¹ *Pflüger's Arch.* LXVII. p. 443. 1897.

² *Amer. Journ. Physiol.* II. p. 203. 1899.

³ *Pflüger's Arch.* CXXXVII. p. 59. 1910-11.

⁴ *Ibid.* CXXIV. p. 198. 1908.

⁵ *Zntrlb. f. Physiol.* XXIV. p. 927. 1910.

I have made ten experiments, in which the splanchnic nerves were cut on both sides, so as to avoid the central effects of ether, and in which electrical stimulation was applied to the nerves of one side either above or below the diaphragm.

It should be remarked that when the sympathetic nerves were stimulated within the thorax, the main trunk was used for convenience of its length and consequently the preganglionic fibres, not only of the splanchnics but also of those running for some distance down the lumbar sympathetic chain, were excited so that erection of hairs over the rump was caused. This did not introduce any serious error into the various experiments.

Faradisation was used for from three to seven hours, periods of stimulation for a few minutes alternating with those of rest, and the blood-pressure being always observed to make sure of the potency of the stimulus. The effect on the glands was very slight.

For example:

- (52) Ether for 8 hours. Both splanchnics cut within thorax: right faradised for 7 hours, 7 minutes on and 3 minutes off. Even at the end of the experiment stimulation of the splanchnic caused the blood-pressure to rise from 80 to 110 mm.

Right $\cdot 25$ gm. = $\cdot 21$ mgm.

Left $\cdot 25$ gm. = $\cdot 32$ mgm.

When, instead of faradisation, rhythmic stimuli were thrown in at the slow rate of one a second, the effect was still less.

Nor was any better effect seen when the nerve was faradised continuously for a period of two hours: the loss then, indeed, was almost inappreciable.

On *dogs* I have made only four observations, which accorded closely with those on the cat.

- (53) Large dog. Ether for 6 hours. Left splanchnics cut. Blood-pressure steady at 110 mm.

Right $\cdot 71$ gm. = $\cdot 81$ mgm.

Left $\cdot 705$ gm. = $1\cdot 35$ mgm.

This illustrates the simple effect of ether anæsthesia, precisely as in the cat. To avoid this error, both splanchnics were next cut within the thorax, and faradisation applied to the nerve of one side or the other. Hardly a trace of exhaustion was produced.

- (54) Small dog. Ether and chloroform. Both splanchnics cut within thorax. *Right* faradised for 3 hours, 3 minutes on and 2 minutes off, with occasional longer intervals for recovery. Blood-pressure generally rose from 100 to 160 or 170 mm.

Right $\cdot 50$ gm. = $\cdot 67$ mgm.

Left $\cdot 47$ gm. = $\cdot 69$ mgm.

- (55) Medium sized dog. Ether. Both splanchnics cut within thorax. *Left* faradised for $3\frac{1}{2}$ hours as above. Reaction of blood vessels good and sustained: even at end of experiment blood-pressure rose from 80 to 120 mm. (Cf. Fig. 7.)

Right $\cdot 8$ gm. = $1\cdot 3$ mgm.

Left $\cdot 66$ gm. = $1\cdot 4$ mgm.

- (56) Small dog. Ether and chloroform. Both splanchnics cut within thorax. *Left* faradised *continuously* for $1\frac{1}{2}$ hours. Blood-pressure reaction was fatigued sooner than the erection of hairs over the rump.

Right $\cdot 36$ gm. = $\cdot 75$ mgm.

Left $\cdot 36$ gm. = $\cdot 65$ mgm.

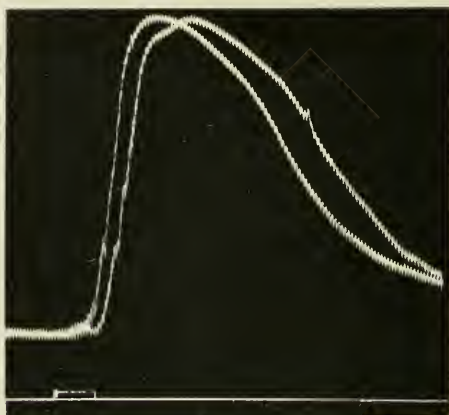


Fig. 7. From Exp. (55). Dog: both splanchnics cut, and left faradised for $3\frac{1}{2}$ hours. Each gland yielded an extract of almost identical strength, A and B being $0\cdot 5$ c.c. of each.

So slight is the change in the residual adrenalin caused by faradisation of the splanchnic nerves, that it would never have sufficed to convince me of the existence of the splanchnic control. But the experiments of Dreyer and of Tscheboksaroff, showing that adrenalin appears in increased quantity in the suprarenal venous blood when the splanchnics are stimulated, experiments that are of a delicate nature and that I have not attempted to repeat, do seem to prove that electrical excitation of the nerves causes excretion of adrenalin. This escape of adrenalin into the blood was illustrated by the investigators, whom I have quoted, by injection of the venous blood into a second animal and so proving its increased percentage of adrenalin.

But it can also be demonstrated by the reaction of the muscles of the same animal itself, either by those of the blood vessels or elsewhere. Asher's method proves it for the blood vessels, insomuch as excitation

of the splanchnics after removal of the abdominal viscera, that is of the muscles reacting directly to splanchnic stimulation, causes a rise of blood-pressure, but fails to do so when the suprarenals have also been removed. Several years earlier I had attempted identical experiments and with a like result, but did not regard them as sufficiently convincing for publication because the blood-pressure rise produced from the suprarenals, like that in Asher's series, was never as much as 20 mm. A rise of 15 mm. is too near to the limit of error. Since Asher's preliminary communication appeared¹, I have repeated the experiments and find his results to be definite and certain. In a pithed cat, a blood-pressure rise of 40 or 60 mm. can easily be obtained from the suprarenals. That is indubitable. My earlier failure was largely due to the fact that I had worked with ether anaesthesia, which reduces the difference to the low value given by Asher for rabbits. An example is:

- (57) Small cat. 10.0 a.m. Pithed, brain and upper half of spinal cord being completely destroyed. Thorax opened, and both sympathetic trunks cut and placed on one shielded electrode.
- 10.15. Paradise both splanchnics, coil 17 cm. Blood-pressure rose from 48 to 166.
- 10.25. Remove intestines and kidneys. No loss of blood.
- 10.37. Stimulate splanchnics, coil 17 cm. Latent period of 13 seconds, and then rise from 36 to 84. No escape to body muscles, but rump hairs raised. (Cf. Fig. 8.)
- 10.43. Squeeze left suprarenal: no rise of blood-pressure.
- 10.45. Stimulate splanchnics again. Rise from 40 to 96.
- 10.48. Excise both suprarenals, taking care to preserve splanchnics.
- 10.55. Stimulate splanchnics, coil 17 and then at 0. Blood-pressure unchanged at 26, but rump hairs well raised.
- 11.15. Inject .02 mgm. adrenalin. Blood-pressure rise similar to that at 10.45.

The observation was repeated in five different experiments, and was always entirely successful with pithed cats: a pressure rise of 66 mm. was the maximum, and 34 the minimum produced from the suprarenals, and there was always the same latent period².

Next I sought for evidence in the reaction of other muscles than those of the blood vessels. This is admirably provided by the denervated dilator pupillæ, because the iris and associated sympathetic muscular structures respond, after excision of the superior cervical ganglion, with greatly increased sensitiveness to minute quantities of

¹ *Zntrlb. f. Physiol.* xxiv. p. 928. 1910.

² Since the above was written, Prof. Asher has published the full account of his experiments in *Ztschr. f. Biol.* LVIII. p. 274. 1912. No tracings are reproduced. The blood-pressure figures certainly do show the effect of the suprarenal excretion, though as a matter of fact none are higher than the low figures which I had obtained in my own earlier experiments and thought to be inconclusive.

adrenalin. Such enhanced reaction is best seen a week or so after the ganglion has been excised. Then, peripheral stimulation of the cut splanchnics within the thorax, the cat being under ether and its blood-pressure recorded from the femoral artery so as to avoid inequality of circulation through either orbit, leads to the following results. For eight or nine seconds after the onset of the stimulation, as measured by the beginning of the blood-pressure rise, the eyes look alike, for ether anæsthesia generally induces a lobbing forward of the nictitating membrane on the sound side like that over the paralysed eye. Then suddenly the nictitating flashes back, the pupil dilates till the iris is a mere rim to the great, black globe, and the palpebral aperture is driven widely open. The normal eye remains unchanged.

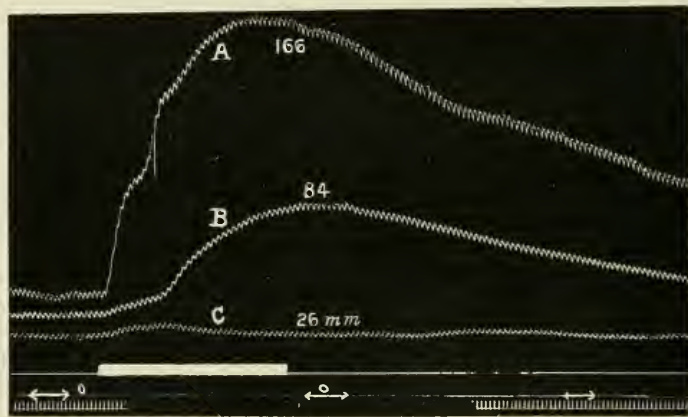


Fig. 8. From Exp. (57). Pithed cat. (A) Stim. both cut splanchnics, rise of 118 mm. (B) Ditto, after removal of abdominal viscera, rise of 48 mm., with longer latent period of 13 seconds. (C) Ditto, after removal of suprarenals; no rise, bl.-pr. 26. Drum was turned back between each, and stimulus always thrown in at the same time on the curve. Seconds marked below.

All these phenomena of sympathetic excitation persist for some time after cessation of the stimulus and fall of blood-pressure, and they are identical in character and time relations with those following intravenous injection of a small amount of adrenalin. Next, in the same cat, the suprarenals are quickly excised, either by a lumbar extraperitoneal incision or through the abdomen, and the splanchnics are again excited. The blood-pressure rises as high as before, but the denervated eye is almost irresponsive. The eyelids do not move at all, though the pupil dilates slightly and the nictitating is withdrawn

slowly and with more delay, the reaction soon vanishing with repetition. The contrast between the results before and after excision of the suprarenals is very great. It may be that the second effect, slight though it be, is similarly due to adrenalin, liberated from other paraganglia or from the actual processes of nervous excitation; or it may be from other metabolites. That the first and chief reaction is caused by suprarenal excretion seems to be beyond doubt.

The prettiest form of the experiment is that in which the suprarenal is excised only on one side: then faradisation within the thorax of the contralateral splanchnic causes full dilation of the pupil, whereas the ipsilateral and glandless nerve can evoke no such reaction at a distance¹.

Other metabolites probably can cause a reaction from the denervated pupil. Asphyxia does not readily do it in the adult cat, and the great "paradoxical pupillo-dilation" that was also observed in the early stages of etherisation in two out of the three adult cats, on which I made these experiments, was probably to be ascribed to their struggling alarm and its attendant emotional excretion of adrenalin when the ether was forcibly administered. But in the kitten asphyxia has been shown to cause paradoxical pupillo-dilation. At the time when Anderson's² experiments on this question were published, I supposed that his results might be explained by an excretion of adrenalin. To test the hypothesis I excised the suprarenals from a kitten. Before the operation light anæsthesia had readily produced paradoxical pupillo-dilation: subsequently it failed to do so, though deep anæsthesia was still effective.

In an adult cat the right superior cervical ganglion was excised, and the eye of that side in the days following was seen to react with great sensitiveness, being paradoxically dilated even in the slight anger shown by the animal when a stranger approached its cage. The suprarenals were then both excised by the lumbar route. Twenty-four hours later, while the cat was still strong and its rectal temperature normal, it was made angry; but not a trace of paradoxical dilation resulted. Light asphyxia was equally without effect. When, however,

¹ Since this paper was sent to the press, I have read the note by Joseph and Meltzer, *Amer. Journ. Physiol.* xxix. *Physiol. Proc.* p. xxxiv. 1912, describing a similar experiment in the rabbit. Their argument was not completed by the removal of the suprarenals, but the American authors have anticipated me in providing this good illustration of the excretion of adrenalin. Judging from their description, the reaction is not so evident in the rabbit as in the cat.

² This *Journal*, xxx. p. 290. 1903.

the animal was deeply asphyxiated to death, a dilation of the right pupil was caused in the terminal spasms.

These experiments of 1904 were not published, because the results seemed to me then somewhat inconclusive. The paradoxical effect was certainly very much depressed by removal of the glands, but that I was inclined to attribute to the harmful shock of the operation and not to lack of adrenalin, because the reaction could be attained with deep asphyxia. Now fuller knowledge makes it clear that excretion from the suprarenal glands is the cause of nearly all the phenomena of paradoxical pupillo-dilation that have been studied by various workers. Still, these old experiments have interest in respect of the present discussion because they prove that the suprarenals are not in absolutely all cases responsible for such paradoxical effects, which may appear in deep asphyxia although the suprarenals have been removed.

Attention to the blood-pressure records in the course of these experiments led, to my surprise, to another observation of interest. A well-known characteristic of the pressure curve seen when the splanchnics are stimulated under good conditions in the cat, is that it rises rapidly for nine or ten seconds; then, without any check in the heart's rhythm, the curve is sharply cut down nearly to the level from which it came, whence it rises slowly again so long as the stimulus is continued. The cusp of the curve always is placed at the same time interval from the beginning of the rise, and the instant of the turn is that very moment when the nictitating membrane and other structures of the denervated eye first move. The drop is, paradoxically, due to the liberation of adrenalin into the blood. Further proof of this is given in the detailed experiments that follow:

(58) In an etherised cat, from which the superior cervical ganglion had been excised 8 days previously, both splanchnics were cut above the diaphragm. Their stimulation yielded the typical result, pressure rising from 140 to 164, a sharp drop to 120, and then a slow rise to 150. Exactly at the turning point from 164 the nictitating and iris reacted on the denervated side. Both suprarenals were then excised by opening the abdomen, the viscera being covered with hot, moist flannels. The abdomen was closed, and the splanchnics again stimulated. Pressure rose from 130 to 170, steadily and without any secondary drop: the nictitating moved back very slowly and the iris dilated just a little. Repetition gave always the same type of blood-pressure curve, an absolutely even rise that was uniformly upheld on a smooth plateau.

Next a small dose of adrenalin, .005 mgm., was injected into the cat's jugular vein. A slow rise of blood-pressure resulted. The splanchnics were stimulated: a smooth rise again. Finally the same dose of adrenalin was injected into the jugular, and at the same moment the splanchnics were faradised. The curves of blood-pressure rise did not add up to a higher level, but a switchback curve of rise and fall and rise was produced, just like that seen with splanchnic excitation and intact suprarenals.

The success of these experiments depends upon the condition of the animal. Section of the vagi makes no difference to the result. In cats that have been admitted to the laboratory overnight and are still alarmed by their strange surroundings, a condition in which the suprarenals are always found to be somewhat exhausted of adrenalin (cf. p. 379), excitation of the splanchnics rarely produces a secondary fall in the blood-pressure: indeed, then, the pressure curve more often shows a slight secondary rise at the moment when adrenalin should be

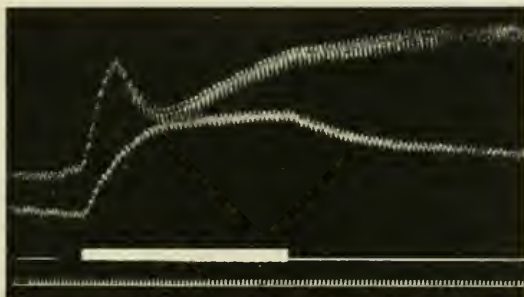


Fig. 9. Etherised cat. Upper curve, stimulation of both cut splanchnics within thorax: bl.-pr. 70-120-96-130. Suprarenals then excised and both splanchnics again stimulated: lower curve, 50-92 upheld.

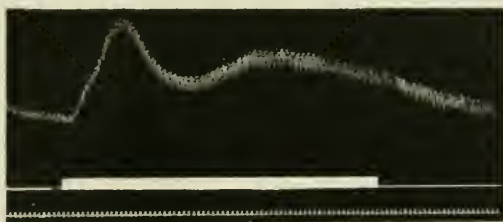


Fig. 10. From same Exp. as Fig. 9. After excision of the suprarenals, the splanchnics were again stimulated and adrenalin was at the same time injected into the jugular vein. The curve closely resembles the upper one in Fig. 9 before excision of the glands.

entering the circulation. Best results are obtained with animals that purr when stroked, and generally manifest a sense of *bien être*. In such (cf. Exp. 59), a clear drop is always seen with splanchnic stimulation, and is often caused too by the simple injection of a minute quantity of adrenalin itself, when the pressure is standing fairly high. From a very low pressure, as in a pithed animal, the splanchnics cause no drop at all but simply a big rise (cf. Fig. 8). Therefore, that the

the secondary fall indicates a stimulation of vaso-dilator fibres coincidently with, and at last prepotently over, the vaso-constrictors. That may be so, or not. For the present argument it is enough to recognise that this well-known drop in the curve, when the splanchnics are stimulated, is caused by the discharge into the blood of suprarenal secretion. How the drop is caused, whether it be a matter of vaso-motor balance, or the signal of a more subtle play between adrenalin and nervous excitation, that is a question lying beyond.

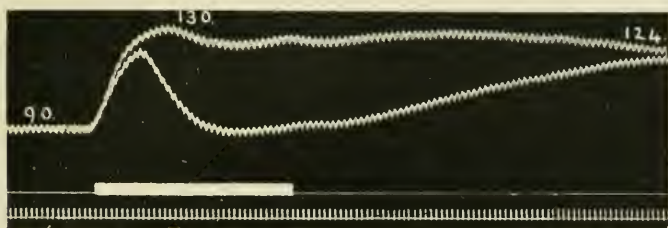


Fig. 11. From Exp. (59). Etherised cat. Both splanchnics cut within thorax. Left suprarenal excised. Upper curve, stim. left (glandless) splanchnic: bl.-pr. 90-130-124. Lower curve, stim. right splanchnic: bl.-pr. 90-122-88-124. Time marked in seconds.

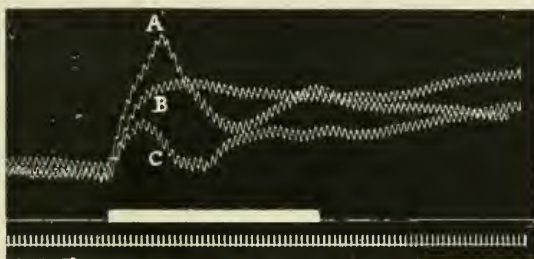


Fig. 12. From Exp. (59). (A) Stim. right spl. 90-152-114-130. (B) Stim. left (glandless) splanchnic, 90-132. (C) Stim. left splanchnic, and inject .005 mgm. adrenalin into subclavian artery; bl.-pr. 90-106-92-110.

Various explanations might serve for the anomaly that prolonged electrical excitation of the splanchnics fails to cause exhaustion of residual adrenalin to anything like the same degree which is attained in the reflexes from the central nervous system.

The glandular nerves certainly do react to the artificial stimulus of faradisation, but it may be that they soon become irresponsive. Or the nerves stimulated may be only excretory, and so fail of action when no more material lies within their immediate grasp, whereas in the nervous

reflexes the whole machinery is used to feed the excreting nerves. Or again, it may be urged that the nerves contain anabolic as well as excretory fibres, and that both are excited together when the trunk is directly faradised. Opposed to the last view are the following considerations:

(a) Days after section of the splanchnics on one side, no difference is found in the adrenalin content of the two glands, when the cat is resting quietly. Anabolism seems to proceed without central control, and both are fully loaded. The decentralised gland in all experiments was found to contain as much or more adrenalin than its fellow.

(b) It is improbable that coarse faradisation should strike so even a balance in the excitation of anabolic side by side with excretory fibres, that but little difference should appear between the two glands, and that yet a great difference should be so readily manifested in every prolonged nervous reflex.

(c) Stimulation of one splanchnic does not cause any difference between the cortical cells of the two glands.

The question remains undecided. Adrenalin does escape from the suprarenals into the blood stream, and that escape is controlled by the splanchnic nerves.

THE REFLEX NATURE OF THE SPLANCHNIC CONTROL.

Electrical excitation of various afferent nerves will induce reflex exhaustion of residual adrenalin very rapidly, and that too though the reflex is not necessarily one associated with high rise of blood-pressure.

(60) Ether. Left splanchnics cut within thorax. Left sciatic nerve faradised at intervals for 4 hours. Blood-pressure rise only 20 mm.

Right .47 gm. = .04 mgm.

Left .45 gm. = .34 mgm.

Such exhaustion developed sooner than would have been the case with ether anæsthesia alone. The reflex occurred at a level at least as high as the vaso-motor centre in the medulla oblongata, for it was never obtained when the spinal cord was transected at a plane above the origin of the splanchnic efferent nerves¹.

¹ This failure of the suprarenal reflex agrees with Sherrington's observation of the difficulty of exciting any ordinary vaso-motor reflexes from the spinal cord. (*This Journal*, xxxviii. p. 380. 1909.)

- (61) Ether. Spinal cord transected at the first thoracic segment. Left splanchnics cut within thorax. Sciatic and other afferent nerves stimulated in succession for 1 hour. Good reflexes of the body muscles: blood-pressure only 40 mm. and practically no rise with reflexes.

Right .17 gm. = .19 mgm.

Left .18 gm. = .19 mgm.

- (62) Decapitated, and cord severed at second cervical. Left splanchnics cut within thorax. Various afferent nerves faradised for 1 hour: brisk bodily reflexes, but blood-pressure rose only 20 mm.

Right .29 gm. = .15 mgm.

Left .27 gm. = .12 mgm.

In the same way, it was found that, after pithing the brain, transection of the spinal cord at the first thoracic segment prevented the usual exhaustion by the splanchnic nerves. The experiments with β -i prove that low blood-pressure in itself does not check the nervous exhaustion.

The level of the mechanism controlling the suprarenals, at which this afferent reflex occurs, is not higher than the corpora quadrigemina.

- (63) Ether. Skull trephined, and cerebral hemispheres removed entirely after transection just above the anterior corpora quadrigemina. Ether then stopped: left splanchnics cut within thorax. Spontaneous respiration, and lively reflexes. Blood-pressure 150. For next 2 hours the central ends of the sciatic and other afferent nerves were faradised, so as to produce strong skeletal muscle reflexes, and blood-pressure rise of 60 or 70 mm. each time.

Right .27 gm. = .01 mgm.

Left .26 gm. = .15 mgm.

The cat had been in stock 4 days: both glands were partly exhausted by the first $\frac{3}{4}$ hour dissection of the brain, and then exhaustion of the right gland was completed in the next two hours' reflex stimulation after the left nerves had been cut.

Apparently the reflex control of the suprarenals is associated with the nervous machinery in the neighbourhood of the vaso-motor centre which governs other sympathetic emotional musculature.

Hæmorrhage. A few experiments were made upon the immediate effects of copious hæmorrhage, to see whether under such conditions an increased drain upon the suprarenals would be associated with the vaso-motor reflexes. When an etherised cat is bled 30 c.c. or more, the blood-pressure falls abruptly: in a few minutes it is picked up again by a strong vaso-constrictor action. Repetition of the hæmorrhage reduces the blood-pressure to a low level, and the animal's brain becomes very torpid so that hardly any anæsthetic is needed to maintain complete quietude. The bodily reflexes are lessened, but, of course, not

extinguished; and the same holds true for the vaso-motor reflexes. Exhaustion of residual adrenalin was evidenced in the usual way by section of the splanchnics; but it did not appear to be much greater than would be caused under ether anæsthesia and the ordinary conditions of experiment.

REMARKS.

A broad review of the facts put forward in this paper sees their agreement with those of other workers in proving that there is a very sensitive and prompt control by the nerves of adrenalin excretion from the suprarenal glands. Adrenalin has justly been included in the catalogue of the hormones, but, in default of fuller knowledge, such classification rather tended to suggest that its secretion and consumption would proceed steadily and inevitably as one of the chemical adjustments of the body that are transacted automatically below the level of nervous control. This idea was not explicitly laid down in Starling's general view of the hormones, and it is most emphatically not true in respect of adrenalin. The vertebrate animal controls a widely distributed field of plain muscle directly through the sympathetic efferent nerves. Intimately connected with these efferent nerves are the paraganglion cells of the suprarenal, secreting the hormone, adrenalin, which can evoke a response from the peripheral muscles identical with that to the nervous impulse. In the various reflex actions of the vaso-motor centre the gland cells also are involved. The efferent path from the bulbar centre to the muscles is twofold—directly by nervous impulses to the muscles, and indirectly by nervous impulses to the suprarenals, whence the chemical messenger, adrenalin, is despatched to the same muscles almost contemporaneously with the nervous impulses. The nature of this double action has never yet been analysed, though it may contain the essential secret of nervous activity. Very suggestive are two features of the interaction; firstly, that the response of a muscle to adrenalin is quickest when the muscle is one that is being incessantly played on by the direct nervous reflexes of daily life¹; and secondly, that removal of the suprarenals leads to atony and nervous paralysis in those muscles which have actually been made use of in nervous reflexes by the animal after loss of the glands². It is my hope to bring forward experiments dealing with this question in a later paper.

¹ This *Journal*, xxxii. p. 426. 1905.

² *Ibid.* xxxi. *Proc. Physiol. Soc.* p. 20. 1904.

SUMMARY.

By measurement of the amount of adrenalin that can be extracted from the suprarenal glands of the cat, it is proved that:—

(1) The suprarenal glands contain almost exactly equal amounts of adrenalin on each side.

(2) The fright induced by morphia or β -tetrahydronaphthylamine exhausts the residual adrenalin.

(3) All ordinary conditions of anæsthesia, with ether, or chloroform, or urethane, are attended by exhaustion of adrenalin.

(4) Excitation of afferent nerves, such as the great sciatic, or direct injury to the brain, whether by simple pithing or by faradisation, also causes loss of adrenalin.

(5) The centre controlling such loss is close to the bulbar vaso-motor centres.

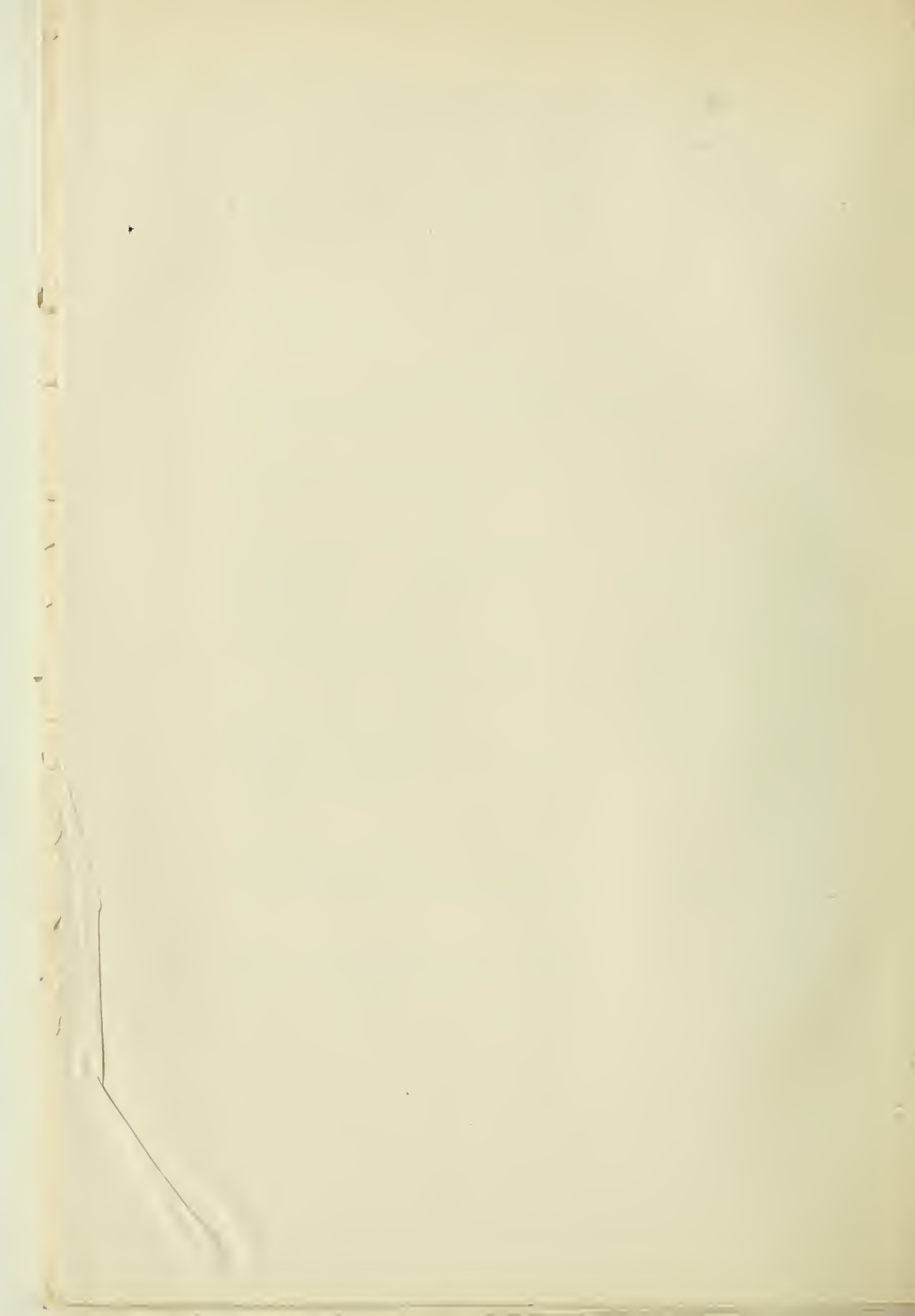
(6) The efferent path is by the splanchnic sympathetic nerves. Their section prevents this exhaustion; and ether, chloroform, and other drugs, such as pilocarpine and physostigmine, or even diphtheria toxin, appear to have no exhausting action directly on the suprarenals¹.

(7) Faradisation of the splanchnic nerves discharges adrenalin into the blood, causing a characteristic drop in the rising curve of blood-pressure, and such phenomena as paradoxical pupillo-dilation.

From the variety of methods and the rapidity with which such adrenalin loss can be induced through the splanchnic nerves, it appears probable that the suprarenal glands are played upon by the splanchnic nerves in the emotional and vaso-motor reflexes with almost as delicate and everchanging an adjustment as are the muscles of the peripheral tissues connected with the sympathetic nerves.

¹ Ultimately, however, the glands must be capable of automatic excretion, for the decentralised gland suffices to keep the animal alive. If in a cat the suprarenal on one side be removed, and the splanchnic nerve of the other divided, the cat does not die until the second suprarenal has also been excised.

This work was carried out in the tenure of a Beit Memorial Fellowship. A grant toward its expenses had previously been received from the Royal Society.



THE FUNCTIONAL AND HISTOLOGICAL EFFECTS OF INTRANEURAL AND INTRAGANGLIONIC INJECTIONS OF ALCOHOL.

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Since its introduction by Schlosser¹ in 1903, the injection of alcohol into nerves for the treatment of neuralgia and other painful conditions has become a well-established therapeutic measure. In his earlier paper² he recommended its use, not only for sensory, but also for motor and mixed nerves, especially the facial in "tic convulsif," and the sciatic in "sciatica." In the case of motor and mixed nerves, however, he aimed, not at actual penetration, but only at injection into the neighbourhood of the nerve, a procedure which produced a paralysis lasting only half an hour to one hour. In a later paper³ he states that 80 per cent. alcohol applied locally to a nerve-trunk produced degeneration and absorption of all parts except the neurilemma. He gives no details of the histological

The animals employed were, with one exception, cats. In all cases they were fully anaesthetized during the operations, which were carried out with strict antiseptic precautions. The nerve or ganglion was exposed by careful dissection, and the alcohol injected obliquely from a syringe fitted with a fine needle. The excess of fluid was lightly mopped out, and the wound closed.

Histological Stains Employed.

1. For a general survey, extent of fibrosis, etc.—(a) Delafield haematoxylin and eosin, (b) Weigert haematein and Van Gieson.
2. For nerve cells—Unna's polychrome blue method.
3. For the medullary sheaths—Marchi's method, counter-stained, in some cases, by Macco's eosin and methyl blue mixture.
4. For the axones—Cajal's and Bielschowsky's silver impregnation methods.

GROUP 1.—INJECTIONS INTO THE INFRAORBITAL NERVE.

Four experiments of this nature were performed, as follows:

EXPERIMENT 1.—Cat. Floor of right orbit exposed, and 0.5 c.cm. of 80 per cent. alcohol injected into (?) the infraorbital nerve.

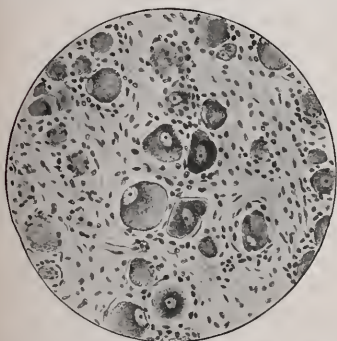


FIG. 1.—Cat 2. Part of section of Gasserian ganglion (polychrome blue), showing chromolysis of some of the cells. (Drawn under $\frac{1}{2}$ in. objective.)

examination, nor any statement as to how deeply the penetration had occurred. In this same paper he gives statistics of 202 cases, including 38 of sciatica and 9 of tic convulsif (all the latter recurred in three to seven months), and adds a warning as to the danger of producing motor paralysis.

The only other experimental work on the subject which has come under my notice is that of Finkelburg,⁴ who injected 0.5 to 1.5 c.cm. of 60 to 80 per cent. alcohol into the sciatics of dogs. A complete paralysis of the corresponding muscles was produced, remaining marked for months. Microscopically, an almost complete degeneration of the nerve bundles was found. If the injections were made only into the neighbourhood of the exposed nerve and the wound closed, well-marked motor weakness resulted, lasting several days. Examined by the Marchi method after fourteen to twenty-one days, the outermost bundles of the nerves showed a high degree of degeneration; in the central parts there was considerable blackening; in addition, further off, were some slight "stippling"; in addition, further off, were some slight haemorrhages under the sheath. The axones do not appear to have been examined.

The present paper deals with the functional and histological results obtained by alcohol injections into various nerves and ganglia. The experiments may be divided into three groups, as follows:

1. Injections into a pure sensory nerve—the infra-orbital.
2. Injections into the Gasserian ganglion.
3. Injections into mixed nerves—the sciatic and the anterior crural.

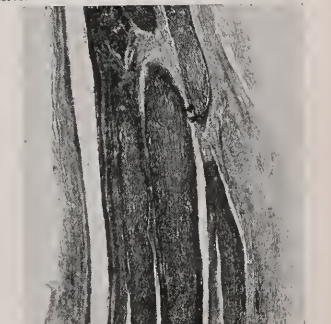


FIG. 2.—Cat 2. Section of part of infraorbital nerve from the floor of the orbit (haematein and Van Gieson) (photograph $\times 40$), showing the bundles of degenerated nerve fibres embedded in newly formed fibrous tissue.

The animal was again anaesthetized seventeen days later, and both infraorbital nerves stimulated by the faradic current at their points of exit from the foramina. No difference could be detected in the result on the two sides. The animal was then killed and the nerves, etc., examined as below:

Macroscopically, a tract of haemorrhage was seen on one of the branches of the nerve on the floor of the orbit.

Microscopically, no obvious changes were found either in the Gasserian ganglion, or in the parts of the infraorbital nerve central and peripheral to the point of injection. Sections at the site of haemorrhage showed a considerable amount of blood lying round the bundles of the nerve, but no obvious change in the bundles themselves.

The intracerebral roots of the nerve showed no trace of degeneration.

EXPERIMENT 2.—Cat. Experiment as in 1.

Twenty-one days later the animal was again anaesthetized and both infraorbital nerves stimulated. The left produced the usual reflex quickening of respiration, the right practically no effect.

The post-mortem examination showed that the nerve in the floor of the orbit was embedded in dense fibrous tissue firmly adherent to the bony floor.

Microscopically, the results were as follows:

(a) Gasserian ganglion.—Some groups of cells showed definite chromolysis, with eccentricity or disappearance of nucleus,

* Except in Experiments 3 and 4, in which the alcohol was injected without preliminary dissection.

breaking up of the chromatin granules, etc. (Fig. 1). These cells were chiefly in the part of the ganglion adjacent to the middle division, but some were scattered among other groups of cells.

(b) The part of the infraorbital nerve in the scar showed great fibrosis with implication of the bundles to varying degrees and corresponding destruction of nerve fibres (Fig. 2).

(c) Proximal to this the nerve was apparently normal (both axones and sheath).

(d) Distal to the scar the nerve was completely degenerated; no normal fibres could be seen, and the axones had practically entirely disappeared. There was great proliferation of the nuclei of the sheath.

(e) The intracerebral roots showed no degeneration.

EXPERIMENT 3.—Cat; 0.5 c.cm. of absolute alcohol injected through the skin into the left infraorbital foramen (under ether anaesthesia).

On the following day there was some protraction (paralysis) of the corresponding palpebral membrane, which passed off in the course of a day or two. No other symptoms were noticed.

Nineteen days later the animal was anaesthetized with ether and both infraorbital nerves exposed distally. On faradic

stimulation the effect on respiration seemed less marked on the left side than on the right.

Microscopically nothing abnormal could be seen.

Microscopically the results were as follows:

(a) Gasserian Ganglion.—

Some cells showed eccentricity of nuclei and disappearance of chromatin; none, however, had the shrunken, deeply stained appearance characteristic of complete destruction.

(b) Infra-orbital Nerve.—

In the anterior part of the floor of the orbit it showed, by Marchi's method, degeneration of the majority of its fibres; some had, however, escaped, and showed the normal appearance. In some of the former group the degeneration appeared incomplete—stretches of normal medulla with scattered globules

of black-staining fat. The proximal part of the nerve at the sphenoidal fissure showed no degeneration.

(c) The brain-stem showed no degeneration.

EXPERIMENT 4.—Cat. Procedure as in (3); symptoms identical.

Twenty days later the animal was anaesthetized with ether, and both infraorbital nerves stimulated as in (3). No definite difference could be observed—that is, respiration appeared to be quickened in both cases.

Microscopically, no obvious change.

Microscopically, the results were as follows:

(a) Gasserian Ganglion.—Changes practically identical with those in Animal 3.

(b) Infra-orbital Nerve.

1. Branches emerging from the foramen. By Marchi's method these showed a very considerable amount of degeneration with some normal fibres left. These nerves were very difficult to tease, due apparently to an increase of fibrous tissue.

2. In anterior part of floor of orbit. Sections stained by haematein and Van Gieson showed destruction of the nerve bundles with some increase of fibrous tissue and considerable round-celled infiltration. One bundle had, however, partly escaped (Fig. 3).

3. The nerve just central to 2. Examined by Marchi's method, many of the fibres showed the junction of the pathological and the normal parts (Fig. 4)—that is, the distal part showed numerous black globules, getting gradually less as the fibre was traced centrally, until a normal medullary sheath was reached. There were more completely normal fibres here than in the more distal part—that is, the alcohol effect had spread back unevenly, having extended further along some fibres than others.

(c) The brain-stem showed no degeneration.

In considering the results obtained in these four experiments one is struck by the fact that in No. 1 the nervous structures completely escaped injury. Apparently the needle entered the nerve, producing the haemorrhage described, but they must have slipped out of it before any alcohol had entered. This is an accident which presumably occurs not infrequently in clinical work, in those cases in which the alcohol fails to relieve the pain, or relieves it only for a very short time. In the three other experiments a considerable effect was produced in each case—a more or less complete degeneration of the peripheral part of the infraorbital nerve. In No. 2, in which the alcohol was injected by the "open method"—that is, after exposure of the nerve by operation—the degeneration was complete, and the whole nerve was found imbedded in dense new fibrous tissue. In 3 and 4, in which the injection was made by the method employed clinically, the degeneration was not complete, though quite considerable in extent. In none, however, had the degeneration "ascended"; the nerve proximal to the part affected by direct contact of the alcohol was in each case normal. The Gasserian ganglion showed a similar change in all three cases—chromatolysis in some groups of cells, but no sign of actual cell death; in other words, no cells exhibited the shrunken, deformed, deeply-staining appearance suggestive of complete destruction. In harmony with this, there was total absence of change in the proximal roots of the trigeminal nerve, both extra- and intracerebral.

The conditions resulting from such injections may be summarized as a local destruction of fibres by the alcohol, with some consequent chromatolytic change in their cells, but without any ascending degeneration or nerve-cell necrosis. Such conditions are comparatively favourable to regeneration, as will be shown below, and this chemical section of the nerve is probably followed more quickly by regeneration than is mechanical section, or, better, resection of part of the nerve.

GROUP II.—INJECTIONS INTO THE GASSERIAN GANGLION. The four following experiments were performed:

EXPERIMENT 5.—Cat. Left Gasserian ganglion exposed by the temporal route, and injected with about 0.75 c.cm. of 80 per cent. alcohol.

Seven days later the animal was killed, and the brain perfused *in situ* with formalin.

Microscopically, the results were as follows:

(a) Left Gasserian Ganglion.—Sections were stained both by polychrome blue and by haematein-Van Gieson. The most marked change was in the part free from nerve cells, that is,

* These operations were kindly performed for me by Sir Victor Horsley, to whom my best thanks are due.

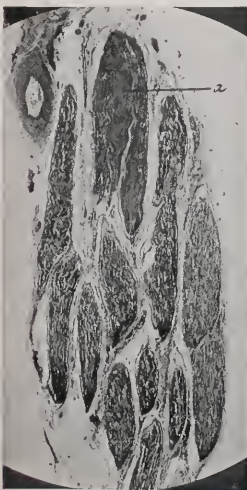


Fig. 3.—Cat 4. Section of part of infra-orbital nerve from the floor of the orbit (haematein and Van Gieson (photograph x 40), showing destruction of the nerve bundles without much fibrosis; one bundle (a) has, however, almost entirely escaped.

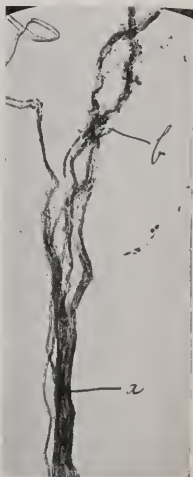


Fig. 4.—Cat 4. Some teased fibres of the infra-orbital nerve (Marchi) (photograph x 80) showing the junction of the normal part (a) with the degenerated part (b).

(c) *Trunk of the Middle Division.*—This showed only a few degenerated fibres.

(d) *Trunk of the Inferior Division.*—This was practically free from degeneration.

(e) *The Root of the Trigeminal (proximal to the ganglion).*—This showed very considerable degeneration, amounting to at least half its fibres.

(f) *The Brain-STEM.*—Here the appearances confirmed (c). The spinal root showed wide degeneration, amounting in the pons to approximately half its fibres. Further back, in the medulla, this proportion diminished, so that at the level of the pyramidal decussation it was about a quarter of the whole.

This experiment confirms the conclusion arrived at from the results of Nos. 5-7, that the alcohol when injected into the ganglion tends to spread centrally to the proximal root without destroying the larger number of cells *en route*. The amount of "central" degeneration was undoubtedly far in excess of the sum total in the three peripheral trunks, and disproportionate to the cell destruction. This raises the interesting question: Are these fibres of the spinal root capable of regeneration? It is usually held that such is not the case, that fibres in the central nervous system, even those of exogenous origin, do not undergo complete regeneration. If this is true, then from the therapeutic point of view a complete section, mechanical or chemical, of the root of the trigeminal nerve proximal to its ganglion, should be equivalent to removal of the Gasserian ganglion itself. I am at present engaged in trying to elucidate how far this is true—to what extent regeneration can occur in the cord after section of posterior roots, etc. Clinical experience is against the view that simple section of the trigeminal nerve proximal to the ganglion is as effective as removal of the latter; the possibility must not be lost sight of, that pain impulses might be carried into the brain by fibres only imperfectly regenerated—for example, fibres which consist of an axone without a morphologically perfect medullary sheath.

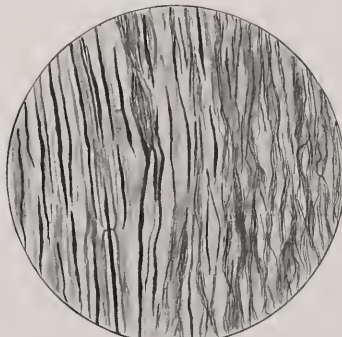


Fig. 8. Cat 13. Section of left posterior tibial nerve (Cajal stain); on the left of the section are seen the normal axones, and on the right the fine, newly regenerated ones. (Drawn under 3 in. objective.)

GROUP III.—INJECTIONS INTO MIXED MOTOR AND SENSORY NERVES.

Eight such experiments were performed, of which the following is a brief summary:

EXPERIMENT 9.—June 28th, 1910. Cat. 0.5 c.c.m. 80 per cent. alcohol injected into left sciatic in lower part of thigh; 0.5 c.c.m. normal saline similarly into right sciatic.

Immediately after operation both hind legs were weak, so that the cat was plantigrade, with both heels to the ground and a tendency to turn the foot over in walking.

July 1st. Right leg practically well; left leg *in statu quo*.

July 27th. Left leg still definitely plantigrade; no sign of recovery. (Cf. photograph, Fig. 7.)

August 12th. Left leg beginning to recover, the heel being slightly raised in walking.

September 27th. (Ninety-one days after operation.) Complete recovery of left leg. At autopsy no macroscopic change was seen in the nerve.

By the Marchi method, a few fibres of the left posterior tibial nerve showed some fine black granules, but most were normal. The rest of the tissues were not examined.



Fig. 7.—Cat 9. Photograph taken a month after injection of alcohol into the left sciatic nerve, showing the weakness of the left hind-leg. Two months later recovery was complete.

EXPERIMENT 10.—June 30th, 1910. Cat. 1 c.c.m. 90 per cent. alcohol injected into left sciatic nerve in mid-thigh.

July 1st. Cat walks with left heel to ground. (Cf. Experiment 9.)

August 3rd. Still in same condition.

August 12th. Leg showing definite improvement; heel beginning to be raised in walking.

August 25th. Walking is now almost normal.

September 26th. (Eighty-eight days after operation.) No difference between the two legs. Cat killed; weights of the two gastrocnemii equal 0.5 grams. Microscopically, the left sciatic nerve looked normal; no inflammatory adhesions were present.

By Marchi method, the left posterior tibial nerve showed some bundles quite healthy, while in others there were slight remains of degeneration in the presence of fine black granules, lying for the most part in "phagocytic" cells between the fibres. The sciatic trunk showed numerous patches of round-celled infiltration, chiefly at the periphery of the bundles; the fibres themselves looked normal.

EXPERIMENT 11.—July 18th, 1910. Cat. 0.75 c.c.m. 50 per cent. alcohol injected into left sciatic in mid-thigh. No weakness of the leg was produced, the animal walking quite well on the following day. It was kept eighteen days without developing any symptoms, and was then killed.

EXPERIMENT 12.—October 26th, 1910. Cat. 0.5 c.c.m. 80 per cent. alcohol injected into left sciatic in mid-thigh.

October 28th. Cat hops slightly, with left heel lower than right.

November 7th. Weakness less marked. November 14th (nineteen days after operation). No difference observable in the two hind legs. Killed. No macroscopic change in the nerve.

Microscopically, there was scattered degeneration in both the peroneal and posterior tibial nerves, involving only a minority of the fibres. The axonal staining showed most axones to be normal, but a few were broken up into irregular fragments.

EXPERIMENT 13.—November 3rd, 1910. Cat. 1 c.c.m. 90 per cent. alcohol injected into and around left sciatic nerve in mid-thigh.

November 7th. Marked ataxia of left hind-leg; left foot is dragged, and the animal tends to walk with the foot turned over, so that the dorsum is in contact with the ground.

December 8th. The calf muscles are greatly wasted.

December 18th. The walking has improved, though the wasting of the calf muscles is still very marked.

January 6th, 1911. The cat walks well, without any obvious ataxia.

Sixty-four days after operation, the left gastrocnemius, tested by Leduc's current (6), showed partial "reaction of degeneration." Right gastrocnemius 30.4 grams; left gastrocnemius 19.4 grams.

Microscopically, the results were as follows:

(a) Left sciatic (above injection, Cajal stain), quite normal. (b) Left sciatic (below injection, Cajal): A patch at periphery of normal large axones; the larger part of the nerve showed disappearance of these, with a few fragments of debris and numerous fine new regenerating axones (Fig. 8). Marchi: Marked advanced degeneration in the greater part of the nerve; a few normal fibres were, however, present.

EXPERIMENT 14.—June 1st, 1911. Cat. 1 c.c.m. 90 per cent. alcohol injected into and around left sciatic nerve in mid-thigh. Very little appeared to have penetrated the nerve.

June 6th. Wound healing well, but cat shows no symptoms at all from the injection.

June 7th (six days after operation). Killed. No macroscopic changes found in the nerve or muscles. No microscopic examination made.

EXPERIMENT 15.—June 1st, 1911. Cat. 1 c.c.m. 90 per cent. alcohol injected into and around left anterior crural nerve just above Poupart's ligament.

June 4th. Marked weakness of the quadriceps extensor of the left thigh.

August 1st. (Sixty-one days after operation.) Very marked wasting and weakness of these muscles.

The cat was anaesthetized and the left rectus femoris examined with Leduc's current. It showed the typical "reaction of degeneration" (complete).⁵ Faradic stimulation

of the trunk of the anterior crural nerve produced no contraction of the muscles. Killed. Weight of right quadriceps, 48 grams; weight of left quadriceps, 20 grams.

Microscopically, the results were as follows:

(a) *The Anterior Crural Trunk*.—At the site of injection the nerve showed profound changes—a massive new formation of fibrous tissue, with patches of rounded infiltration, involving and destroying the greater proportion of the nerve fibres (Fig. 9). A few fibres had escaped, at any rate in these particular sections, but the destruction was very extensive—a veritable "nerve cirrhosis." Above this point, Cajal and Marchi preparations showed a practically normal nerve; the process is a local disorganization, not leading to any ascending change.

(b) *The distal branches* (by Marchi, Cajal, and Bielschowsky methods) showed active preparation for regeneration—the long nucleated protoplasmic columns (the "apoptrophic cells" of Marinesco), without, however, any new axones. It looked as though the marked fibrosis at the site of injection had delayed regeneration, so that the process was slower than, for example, that after successful primary nerve suture.

EXPERIMENT 16.—June 6th, 1911. Cat. 0.5 c.c.m. absolute alcohol injected into and around the left sciatic nerve in mid-thigh.

July 8th. Marked plantigrade gait of left hind foot, with tendency to walk with the dorsum of foot to the ground.

July 26th. Weakness and wasting of the left calf muscles still very marked (fifty days after operation). The cat was anesthetized, and the left gastrocnemius examined with the Leduc current. It showed complete "reaction of degeneration." There was no muscular response to faradic stimulation of the sciatic trunk either above or below the site of injection. The animal was then killed. Weight of right gastrocnemius, 23.2 grams; weight of left gastrocnemius, 8.5 grams.

Microscopically, the results were as follows:

(a) *The sciatic trunk* at the site of injection; the changes were practically identical with those found in the preceding experiment—that is, great fibrosis both between and in the nerve bundles. There were also the remains of numerous haemorrhages in both these situations.

Immediately above this point Cajal preparations showed greater regeneration activity, axones splitting up into complex bundles of fine fibrils, etc. (Fig. 10). Further up the appearances were entirely those of a normal nerve—that is, there was no trace of any ascending degeneration.

(b) *The peripheral branches* showed no new axones—that is, here again the fibrosis had proved a severe obstacle to the downgrowth of new axones from the proximal part. They showed the usual appearances of late Wallerian degeneration—the

presence of numerous comparatively fine fat granules, some being free, others contained in the protoplasm of the invading phagocytes.

A striking feature brought out by a consideration of

these experiments is, as in Group 1, the variability of the results. Thus, in Nos. 11 and 14 the injection produced no obvious effect, in No. 12 only a slight transitory weakness, while in 9, 10, 13, 15, 16 the functional results were severe and more lasting. The technique was, as far as possible, identical in all these experiments, but the strength of alcohol used was not always the same. In No. 11 it was only 50 per cent., which may partially account for the lack of disturbance produced. On the other hand, in both 9 and 14 it was 90 per cent., yet the effects in these two cases afford a striking contrast. There can be not the slightest doubt that the explanation lies very largely in the difficulty of ensuring adequate penetration of the nerve by the alcohol. The texture of the nerve in question has an obvious bearing on this point. The cat's sciatic is composed of several bundles held lightly together by loose connective tissue; such a nerve is more difficult to infiltrate successfully than one of a more compact structure—for example, the posterior tibial. Further, if this difficulty is so prominent when the nerve is exposed by dissection, it becomes still more so when the injection is made through a skin puncture, as is the usual clinical method. On the other hand, when the injection is made into a bony canal (as in the case of the trigeminal), or into a space bounded by dense fibrous structures (as in the case of the Gasserian ganglion), it may well be that the alcohol, by remaining longer in contact with the nerve or ganglion, may produce comparatively more effect, even though little had penetrated during the actual injection.

The muscles supplied by the nerves operated upon in Experiments 9, 10, 13, 15, 16, showed the usual atrophic changes. Identical with those following mechanical section of the nerve. It is interesting to note, however, the fairly rapid recovery which can ensue. Thus, in Experiment 10 this was complete when the animal was killed after

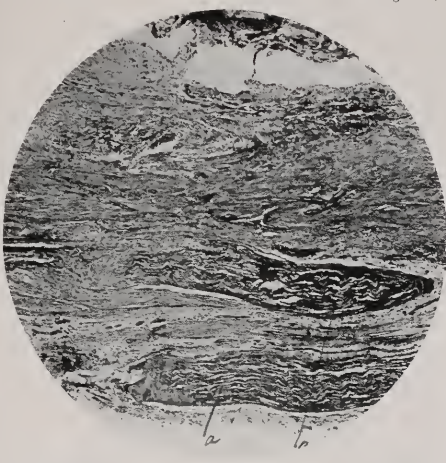


Fig. 9.—Cat 15. Section of the anterior crural nerve at the site of injection (Gaemlein and Van Gieson), photomicrograph $\times 40$, showing profound disorganization of the nerve, with great fibrosis. Two bundles of fibres which have escaped complete destruction are marked (a).



Fig. 10.—Cat 16. Section of the sciatic nerve just above the point of injection (Cajal stain); this shows the axones splitting up into complex bundles of fibrils—a phase of active regeneration. (Drawn under $\frac{1}{2}$ in. objective.)

eighty-eight days. The gastrocnemius muscle weighed the same as that on the control side, and reacted equally well. Moreover, the animal had lost all trace of the limp which was so prominent for some weeks after the operation. Unfortunately, the histological examination was incomplete, as the branches to the gastrocnemius were not examined to see how far they had suffered and how far recovery was due to a true nerve regeneration. In Experiments 13, 15, and 16, however, the investigations were more complete; in 13 (sixty-four days) regeneration was shown histologically to be well advanced, and the muscles had so far recovered that, examined by the Leduc current, they reacted in a manner quite different from the typical reaction of degeneration. In 15 (sixty-one days) and 16 (fifty days) regeneration was much less advanced. In neither of these could any new axones be found in the peripheral branches, and the muscles gave the complete R.D. It is probable that this backwardness, contrasted with 13, is dependent on the greater degree of fibrosis produced by the alcohol in the former, the fibrous tissue forming, as I have found in other experiments, an effective barrier against the downgrowth of the regenerating axones. There is every reason to believe, however, that in due time complete recovery of power would occur in all muscles which had been paralysed by such injections. In other words, there does not seem to be any real danger of permanent paralysis in these cases, though in man the time taken for complete recovery might be a matter of a year or more. This is a matter of some interest, in view of the cases of peroneal paralysis recorded by Schlosser and

others (v.a.) following the treatment of sciatica by these means, though such a procedure is, I fancy, no longer likely to be advocated at the present time.

CONCLUSIONS.

1. Alcohol, injected into the trunk of a peripheral nerve, produces a more or less complete local necrosis of the nerve at the point of injection.

2. The change is not an "ascending" one, the nerve above the point of injection remaining normal; the cells of origin of the fibres may show some degree of chromatolysis, but do not exhibit signs of permanent injury.

3. The conditions produced by such injection are more favourable to regeneration than those resulting from simple section without suture. The anatomical continuity of the nerve trunk favours rapid regeneration, though this is to some extent retarded by the fibrosis which occurs to a greater or less extent in every case of alcohol injection.

4. It is apparently impossible by a single injection of alcohol to produce complete necrosis of the Gasserian ganglion, its dense texture preventing complete infiltration. The alcohol tends to find its way under the sheath of the ganglion towards the proximal root, which is affected to a greater degree than the actual ganglionic cells.

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- ¹ Schlosser, *Klin. Monatsblatt f. Augenheilkunde*, 1903, Bd. 41 (2), s. 244.
- ² *Ibid.*, *Versammlung d. Deutscher Ophthal. Gesellsch.*, Heidelberg, September, 1903. ³ *Ibid.*, *Verhandlung des Congresses f. Innere Medizin*, Wiesbaden, 1907, s. 49. ⁴ Finkelnburg, *ibid.* ⁵ W. Harris, *Lancet*, 1912, vol. 1, p. 218. ⁶ O. May, *Brain*, 1911, vol. xxxiv, p. 272.

A CARDIAC EFFECT OF ADRENALIN IN CHLOROFORMED SUBJECTS.

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In the course of some investigations upon the heart beat in animals under chloroform I have found that adrenalin exerts a very pronounced cardiac effect, and one that has an important clinical significance.

Adrenalin belongs to a group of substances which are styled by pharmacologists "sympathomimetic," of which the action is limited to structures which are innervated by fibres of the sympathetic system. This action is originated in the terminations of the sympathetic distribution, and it results in a rise of blood pressure, mainly caused by vaso-constriction in those vessels in which the constrictor fibres predominate, but also reinforced through stimulation of the augmentor nerves of the heart, which is thereby accelerated and caused to beat with increased force. This direct cardiac action is apt to be overlooked, for it is obscured by the more obvious vaso-constrictor effect, but there is good reason for attributing to it and to it alone the abnormal condition which arises when adrenalin is injected into the blood of an animal under chloroform.

If a small dose of adrenalin chloride, say, half a minim of the commercial 1 in 1,000 solution, be injected into a vein of a cat fully under the influence of chloroform, a well-marked rise of blood pressure will be indicated by a manometer connected with the circulation. If the dose of adrenalin be sufficiently small and the anaesthesia be sufficiently deep, then the heart may be found to continue to beat perfectly regularly; more frequently, however, as the adrenalin effect develops, the heart passes into an irregular condition of a remarkable type. The obvious features of this condition are a rapid succession of small beats, about 300 per minute, the individual beats being sometimes almost equal in size and in time incidence, sometimes more irregular and interrupted by pauses of short duration. Electrocardiographic

tracings demonstrate that this irregularity is one of a singularly complex type—in fact, it frequently happens that not a single normal beat can be found in the sequence, which consists entirely of ventricular extrasystoles; that is to say, the contraction impulses arise in the ventricles themselves and not in sequence to auricular contractions. Moreover, the ventricular contractions are propagated, not from one but from many points of origin in both the right and left ventricles, constituting a condition which may be defined technically as a multiple extrasystolic ventricular tachycardia. After the effect of the adrenalin, which, as is well known, is only temporary, has worn off, the heart quiets down and the beat eventually becomes regular once more.

If the same injection be made into an animal only lightly anaesthetized with chloroform the resulting reaction is ultimately more intense; it is, in fact, almost invariably fatal. To ensure the success of such an experiment the vapour must be reduced below 1 per cent., the corneal reflex being retained and active. We will presume the heart, under such conditions, to be beating with a normal, regular rhythm when half a minim of solution of adrenalin chloride is injected into a vein; the heart passes, as before, into an intensely irregular condition of the type previously described. The final result is, however, different, for before the action of the adrenalin has worn off, and whilst the blood pressure is still abnormally high, the heart, with a startling suddenness, ceases to propel blood into the arterial system, and in a graphic record the blood pressure is seen to sink to zero in the precipitate fashion shown in the tracing (Fig. 1). This is an almost invariable effect. What has happened is this: Up to the moment of the collapse of the circulation the ventricles have been contracting in a chaotic sequence of irregular beats, but each beat is still a *co-ordinate* beat; each ventricle contracts as a whole and expels its contents. The irregularity then advances a step further; the individual muscle bundles of the ventricles, which interlace in many directions, commence to contract *independently* and in sequence, the beat is no longer *co-ordinate*, and as a consequence the ventricles cease to exercise an active function. The ventricles are now said to be “fibrillating”; the electrocardiogram shows a sudden and characteristic change in form; the contraction impulses are still generated, but they are totally disorganized.

The physiological effect of ventricular fibrillation is very different from that of auricular fibrillation—the heart can continue to function in the absence of the auricular systole—in the absence of the ventricular systole the circulation naturally comes to a standstill. Ventricular fibrillation in cats is generally permanent and ends in death of the heart from asphyxia of its tissues, but exceptionally spontaneous recovery occurs, and this may be temporary, culminating in a second collapse (Fig. 2, p. 4), or it may terminate more favourably

in a regular beat and permanent recovery. The prospect of recovery is greater when the doses of adrenalin are very small: the smallest dose I have so far found efficient in a cat has been one-fifth of a minim, and in this case recovery ensued.

The respiratory phenomena in connexion with this form of heart failure are noteworthy—the bulbar centres, which are not depressed as from a full dose of chloroform,

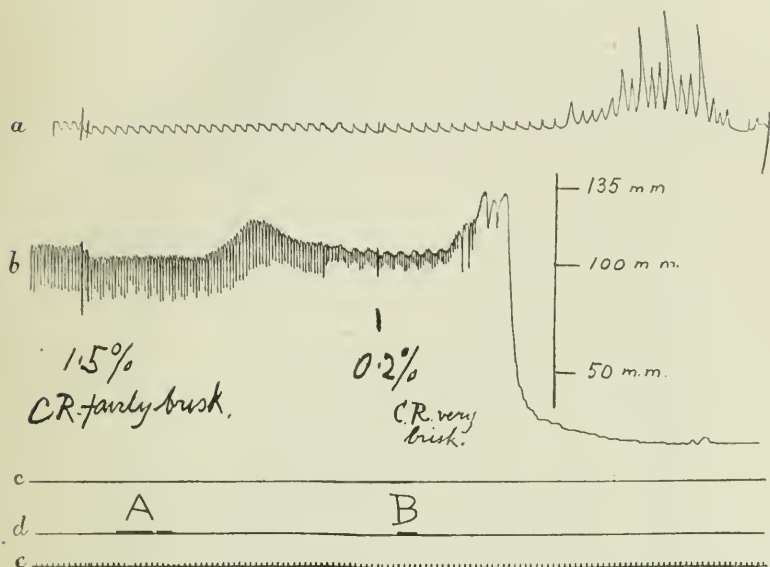


Fig. 1.—*a*, Respiration curve, registered from thoracic movements. *b*, Blood pressure curve, registered by mercury manometer. *c*, Level of zero pressure. *d*, Signal line; each signal mark indicates an intravenous injection of $\frac{1}{2}$ minim of 1 in 1,000 adrenalin solution diluted to 1 in 20,000. *e*, Time marker, indicating intervals of one second. The vertical scale indicates blood pressure levels. The tracing represents the effect of two consecutive injections of adrenalin (*A* and *B*) into the same cat under different depths of chloroform narcosis; *A*, under 1.5 per cent. chloroform; *B*, under 0.2 per cent. chloroform. The result of *A* is a rise of pressure only, the heart beat remaining regular. The result of *B* is likewise a rise of pressure, but with it the heart beat becomes small, rapid (300 per minute), and irregular, and finally ceases abruptly. This cardiac collapse occurs some eighteen seconds after the termination of the injection, and the respiratory movements, after passing through an exaggerated phase, cease also some thirty-eight seconds later.

are suddenly emptied of blood, and the anaemia stimulates the respiratory centre powerfully; a number of deep gasps are taken and then the respiration ceases (Fig. 1). The respiratory centre, however, is not yet dead—it has not been killed by excess of chloroform—spontaneous respirations may arise later, and can be almost invariably evoked by artificial respiration, and the late persistence of respiratory effort in the absence of heart action is a marked feature in many of these deaths.

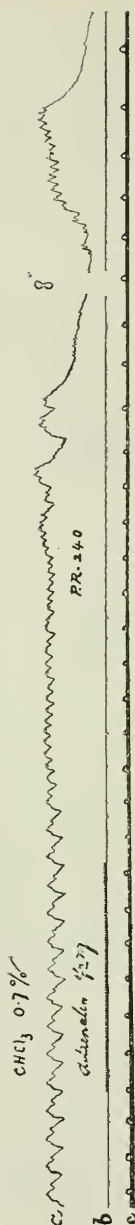


Fig. 2.—*a*, Blood pressure curve registered by Hürtle manometer. *b*, Signal line and level of zero pressure. *c*, Time marker indicating seconds. The gap in the tracing represents an interval of eight seconds. The Hürtle manometer affords a more correct interpretation of the heart beats than the mercury manometer. The drum is moving more rapidly than in Fig. 1, and the character of the individual beats is thus made more distinct. The tracing represents the effect of the injection of $\frac{1}{2}$ minim of 1 in 1,000 adrenalin solution diluted to 1 in 20,000. At the time of injection the heart was beating in pairs (bigeminal beat). The change in the character of the heart beat is well shown. Ventricular fibrillation with total cessation of the heart's action occurs about fourteen seconds after the injection, but in this case temporary recovery occurs eleven seconds later, the gap in the tracing representing a period of eight seconds, during which the heart is inactive. The heart is still irregular on recovery, and fibrillation recurs in four seconds, from which the heart does not this time recover.

In animals not under the influence of any anaesthetic adrenalin does not, in my experience, produce irregularities of the nature I have just described, and under ether I have employed very much larger doses of adrenalin than those which react under chloroform, up to 5 minims of the 1 in 1,000 solution, in fact, with the result that lesser degrees of irregularities were exceptionally observed, and never fibrillation.

In concluding this brief account of experimental work I may remark that I have here merely skirted the fringe of the subject of cardiac irregularities under chloroform, and I must refer those who desire further information to such notes as have already been published on this subject.¹ I have, however, been prompted to anticipate a more complete account by reason of evidence that has recently come to light that this particular reaction of adrenalin under chloroform has an important clinical bearing, as I shall now proceed to show.

The symptomatic effects of an adrenalin reaction in a person lightly under the influence of chloroform may be portrayed as follows: Within a few seconds of the injection the pulse accelerates with a raised tension; it becomes more rapid, is less readily felt owing to diminished excursion, and it may or may not be perceptibly irregular at the wrist; a few temporary pauses may be noted, and then the heart suddenly ceases beating; the pupils dilate widely, and intense pallor supervenes. Respiratory phenomena then follow, a few deep breaths being taken, and then the respirations cease also. A few spasmodic efforts at respiration may be made, or even a short term of regular breathing may be induced by artificial respiration, but the heart still remains impotent. The heart may, however, recover temporarily, still with a small and rapid beat, only to fail once more, and in this way the pulse may be briefly felt *after* the respiratory collapse has occurred. If the cardiac recovery is well sustained the respiration is restored also, only to fail again with the second collapse of the heart. In more favourable cases the heart eventually becomes regular, the breathing is restored permanently, and all goes well.

My attention was first directed to the chloroform-adrenalin reaction in man by a communication made by Dr. Blumfeld, and published in the *Proceedings of the Royal Society of Medicine*, February 3rd, 1911, Anaesthetic Section.

In this case an injection of adrenalin was made into the mucous membrane of the nasal septum, the proposed operation being a submucous resection of a deviated septum. The amount injected was 6 minims of a 1 in 4,000 solution, which is the equivalent of $1\frac{1}{2}$ minims of the commercial 1 in 1,000 solution. The anaesthetic was a chloroform and ether mixture; no anaesthetic was being administered at the moment of injection, and the patient's anaesthesia was light. Sudden pallor and respiratory failure rapidly followed the injection—the pupils dilated, and for a minute or so the patient's condition was serious, but he recovered completely. The condition of the pulse was not noted.

This experience was confirmed by others who took part in the discussion on Dr. Blumfeld's paper, and, further, two fatalities under similar circumstances were referred to. In one of these cases, briefly reported, death followed the injection of a little adrenalin into the tonsils of a patient under chloroform, but of this case I have not been able to obtain further information. The second case was mentioned by Dr. A. L. Flemming, who has kindly sent me further particulars, and these I will give in a later part of this paper.

In the *BRITISH MEDICAL JOURNAL* of February 24th, 1912, there appeared an article by Mr. B. Seymour Jones on anaesthesia for submucous resection of the septum. Mr. Jones has a record of some 100 cases in which adrenalin was injected (in conjunction with cocaine) into several sites on the septum, for the usual purpose of rendering the seat of operation bloodless, the total amount of adrenalin on completion of all the injections being 12 minims. The anaesthetic was a chloroform-ether mixture, and the injections were made when the patient was "barely unconscious." I gather that a not infrequent result of the injection was an "intermittent beating associated with a pulse of a weak and feeble character," and three cases are particularly quoted to illustrate the alarming effects of a sudden absorption of adrenalin. In each of these cases the symptoms noted were intense pallor, cessation of respiration, and dilated pupils; in one case the pulse was felt for, but was not found; in all permanent recovery ensued. In one of these instances the injection consisted of a few drops of adrenalin in $\frac{1}{2}$ c.cm. of normal saline without cocaine. No serious effects were noted in a series of 500 cases in which similar injections were made for operation without any general anaesthetic.

There can be no doubt that in all the foregoing cases the ventricles fibrillated; doubtless the large proportion of recoveries recorded is largely due to a small quantity only of adrenalin passing into the circulation, but their number is remarkable when we take into consideration the deadly nature of the condition of ventricular fibrillation. At one time it was an open physiological question whether fibrillating ventricles ever recovered their normal beat, but the chloroform experiments above referred to definitely settle this question in the affirmative so far as the cat is concerned, although recovery is exceptional. It is evident from these clinical cases that the human heart has a greater capacity for recovery than has the feline heart, but at the same time I have no doubt that this capacity is made to appear greater than it really is through failure to report fatal cases. Apart from the two fatal cases referred to above, I know of none published. Private inquiry has, however, proved more fruitful. Thus:

Surgeon No. 1 had been accustomed to plug the nostrils with adrenalin twenty minutes *prior* to the administration of chloroform for submucous resection of the septum; he had met with no circulatory difficulties whatever.

Surgeon No. 2 had been accustomed to *inject* adrenalin

for the same operation when the patient was lightly under chloroform; and with him my inquiries ceased, as it was unnecessary to pursue them further. This gentleman had "two cases of rapid death after the injection of adrenalin into the nasal septum in cases under chloroform. Both were puny adolescents, one male and one female. In the male a positive diagnosis of status lymphaticus was made; in the female I believe this was not the case." Both cases were lightly anaesthetized, and in both the symptoms were similar. These were as follows: The ischaemia of the septum appeared to spread to the lips and circumoral region, the heart beat violently and rapidly, the pupils became widely dilated, and deep sighing respirations were followed by cessation of breathing. The time relations of these symptoms were apparently not accurately noted, except in so far as that they certainly almost immediately followed the injection. The quantity of adrenalin injected was "a very few drops" of 1 in 4,000 solution with 2 to 3 per cent. novocain. In reply to further questions, he proceeds:

"The peculiar thing is that the very great majority have not shown the slightest disturbance on injection; are some cases especially susceptible? I have been inclined to believe that in the dangerous cases the injection has got directly into the circulation through a small vessel. There is a network of veins at the lower anterior part of the septum in the *submucous* tissue, but one endeavours to inject under the perichondrium, where there are no vessels."

These two cases* afford absolute confirmation of the occurrence of the adrenalin death in human subjects, and that with doses which are extraordinarily small compared with the lethal doses in the cat, having due regard to the relative blood volumes. That the reaction only occurs exceptionally in a series of cases, all treated alike, may be subject to one of two explanations: (a) Presuming adrenalin to be readily absorbed in all cases from submucous tissues, then the reaction may be said to occur in persons abnormally sensitive to small doses; (b) presuming all persons to be equally sensitive to small doses, then the exceptional results may be referred to accidental direct injection into a small vein.

It is difficult to decide definitely on either of these alternatives, and I can only here make a few brief remarks appertaining to this subject. It is well known that on subcutaneous injection adrenalin is, in the generality of instances, only very slowly absorbed, owing to the local vaso-constriction produced; it appears, however, to be certain, from the symptoms entailed, that adrenalin is rapidly absorbed when injected into the gums for dental purposes,² and it is asserted that vaso-dilator fibres predominate in the gums, at least that they do so in the dog, and hence the adrenalin would have a better chance of absorption. I cannot discuss this further, but will proceed to quote a case communicated to

* A precisely similar fatality is reported in the *Leicester Mercury* of August 19th, 1912.

